PATENT SPECIFICATION

NO DRAWINGS

997,638

997,638

Date of Application and filing Complete Specification: March 20, 1962.

No. 10695/62.

Application made in United States of America (No. 97434) on March 22, 1961.

Application made in United States of America (No. 164,615) on Jan. 5, 1962.

Complete Specification Published: July 7, 1965.

Index at acceptance:—C2 C(1E7A, 1E7B2, 1E7C2, 1E7D1, 1E7E1, 1E7F2, 1E7H2, 1E7N5, 1E7P3, 1F1A2, 1F1C2, 1F1C6, 1F1D3, 1F2A2, 1F2C2, 1F2C5, 1F2C6, 1F2D3, 1F3A2, 1F3C2, 1F3C6, 1F3D3, 1F4A2, 1F4C2, 1F4C6, 1F4D3, 1F4F3, 1J1A4, 1J1A5, 1J1C3, 1J2A2, 1J2C3, 1J3C3, 1K2A1, 1K2A2, 1K2A3, 1K2C2, 1K2C3, 1Q2, 1Q3, 1Q4, 1Q5, 1Q6B1, 1Q6C, 1Q7A, 1Q7B, 1Q8A, 1Q8C, 1Q9B, 1Q9C, 1Q9D1, 1Q9D2, 1Q9E, 1Q9F1, 1Q9F2, 1Q9G, 1Q9H, 1Q9K, 1Q9L, 1Q11D, 1Q11G, 1Q11J, 2A1, 2A2, 2A5, 2B2A4, 2B2G3, 2B2J, 2B3A4, 2B3B, 2B3E, 2B3G1, 2B3G5, 2B3G8, 2B14, 2B20, 2B21, 2B29, 2B34, 2B42D, 2B42F, 2B42J1, 2B42J4, 2B43A4, 2B47B4, 2B47D1, 2B47G1, 2B47G2, 2B47G3, 2B47G4, 2B47G5, 2B47G7, 2B49A4, 2B49G3, 2B50A4, 2B50G7, 2D43C, 2D43D, 2D43E, 2D43F, 2D43H, 2D43J, 2D43L, 2D43S4, 2R16, 2T17, 3A2, 3A4, 3A7V1A4, 3A7V1E1, 3A7V1J1, 3A7V1L, 3A7V1Q, 3A7V3A4, 3A7V3E1, 3A7V3J4, 3A8A1, 3A8A4, 3A8B1, 3A8B2, 3A8C3, 3A8D1, 3A8G1, 3A8G3, 3A8K, 3A9, 3A10E3D1, 3A10E5E, 3A10E5F1C, 3A10E5F2A, 3A10E5F3B, 3A13C1C, 3A13C10H, 3A19A4, 3A19B1, 3A19B2, 3A19B3, 3A19C1, 3A19C2, 3A19C3, 3A19D1, 3A19D2, 3A19D3, 3C5A4, 3C5B, 3C5C2, 3C5C3, 3C5C4, 3C5C6, 3C5C7, 3C5E1, 3C5E2, 3C6, B4D, B4M)

Int. Cl.:—C 07 c, d

COMPLETE SPECIFICATION

Indole Derivatives

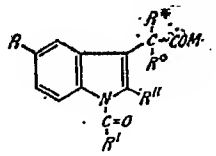
ERRATA

SPECIFICATION No. 997,638
Amendment No. 1

Page 14, line 108, *for* "Examples" *read* "Example"
Page 14, line 108, *after* "3" *insert* "or"
Page 15, line 36, *for* "benzoyloxybenzoyl" *read* "benzyloxybenzoyl"
Page 15, line 42, *for* "benzoyloxybenzoyl" *read* "benzyloxybenzoyl"

THE PATENT OFFICE
13th August 1965

aliphatic acid compounds of this invention have the general structural formula:

I 

atom or a C_{1-5} alkyl, C_{2-5} alkenyl (particularly allyl), phenyl or benzyl radical; R* is a hydrogen atom or a C_{1-5} alkyl or C_{2-5} alkenyl radical or together with R° forms a methylene group doubly bonded to the carbon atom or a cyclopropane ring; R° is a hydrogen atom, except when it is combined with R* to form a methylene radical or a

[*Price*

PATENT SPECIFICATION

NO DRAWINGS

997,638

997,638

Date of Application and filing Complete Specification: March 20, 1962.

No. 10695/62.

Application made in United States of America (No. 97434) on March 22, 1961.

Application made in United States of America (No. 164,615) on Jan. 5, 1962.

Complete Specification Published: July 7, 1965.

Index at acceptance:—C2 C(1E7A, 1E7B2, 1E7C2, 1E7D1, 1E7E1, 1E7F2, 1E7H2, 1E7N5, 1E7P3, 1F1A2, 1F1C2, 1F1C6, 1F1D3, 1F2A2, 1F2C2, 1F2C5, 1F2C6, 1F2D3, 1F3A2, 1F3C2, 1F3C6, 1F3D3, 1F4A2, 1F4C2, 1F4C6, 1F4D3, 1F4F3, 1J1A4, 1J1A5, 1J1C3, 1J2A2, 1J2C3, 1J3C3, 1K2A1, 1K2A2, 1K2A3, 1K2C2, 1K2C3, 1Q2, 1Q3, 1Q4, 1Q5, 1Q6B1, 1Q6C, 1Q7A, 1Q7B, 1Q8A, 1Q8C, 1Q9B, 1Q9C, 1Q9D1, 1Q9D2, 1Q9E, 1Q9F1, 1Q9F2, 1Q9G, 1Q9H, 1Q9K, 1Q9L, 1Q11D, 1Q11G, 1Q11J, 2A1, 2A2, 2A5, 2B2A4, 2B2G3, 2B2J, 2B3A4, 2B3B, 2B3E, 2B3G1, 2B3G5, 2B3G8, 2B14, 2B20, 2B21, 2B29, 2B34, 2B42D, 2B42F, 2B42J1, 2B42J4, 2B43A4, 2B47B4, 2B47D1, 2B47G1. 2B47G2, 2B47G3, 2B47G4, 2B47G5, 2B47G7, 2B49A4, 2B49G3, 2B50A4, 2B50G7, 2D43C, 2D43D, 2D43E, 2D43F, 2D43H, 2D43J, 2D43L, 2D43S4, 2R16, 2T17, 3A2, 3A4, 3A7V1A4, 3A7V1E1, 3A7V1J1, 3A7V1L, 3A7V1Q, 3A7V3A4, 3A7V3E1, 3A7V3J4, 3A8A1, 3A8A4, 3A8B1, 3A8B2, 3A8C3, 3A8D1, 3A8G1, 3A8G3, 3A8K, 3A9, 3A10E3D1, 3A10E5E, 3A10E5F1C, 3A10E5F2A, 3A10E5F3B, 3A13C1C, 3A13C10H, 3A19A4, 3A19B1, 3A19B2, 3A19B3, 3A19C1, 3A19C2, 3A19C3, 3A19D1, 3A19D2, 3A19D3, 3C5A4, 3C5B, 3C5C2, 3C5C3, 3C5C4, 3C5C6, 3C5C7, 3C5E1, 3C5E2, 3C6, B4D, B4M)

Int. Cl.:—C 07 c, d

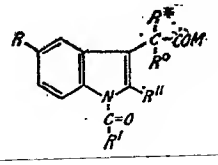
COMPLETE SPECIFICATION

Indole Derivatives

We, MERCK & Co., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to chemical compounds of the indole series. More particularly, it is concerned with new α-(3-indolyl)-lower aliphatic acids having an aromatic carboxylic acyl (i.e. an aroyl or hetero-aroyl) radical of one or two fused rings attached to the nitrogen atom of the indole ring, with salts, esters and amide derivatives of such compounds and with the synthesis of such substances.

The new aroyl and hetero-aroyl indolyl aliphatic acid compounds of this invention have the general structural formula:

I 

in which R^1 is an aromatic radical of one or two fused rings of 5 or 6 atoms each, there being not more than one heterocyclic ring and not more than three hetero atoms, the hetero atoms being oxygen, nitrogen, or sulphur, the aromatic radicals including ketodihydro-aromatic radicals, the enol forms of which are aromatic, and the N-oxides of nitrogen heterocyclic rings, and in which aromatic radicals any substituents are halogen atoms or hydroxy, C_{1-5} alkyl, C_{1-5} alkoxy, phenyl, phenoxy, nitro, C_{1-6} alkanoylamino, di(C_{1-5} alkyl)amino, mercapto, C_{1-5} alkylthio, halo C_{1-5} alkylthio, benzylthio, benzyloxy, phenylthio, halo C_{1-5} alkyl, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, halo C_{1-6} alkanoyl, halo C_{1-5} alkoxy, cyano, di(C_{1-5} alkyl)sulphonamido, carbo C_{1-5} alkoxy, aldehyde, di(C_{1-5} alkyl)-carboxamide, C_{1-5} alkylsulphinyl or C_{1-5} alkylsulphonyl radicals; R^{11} is a hydrogen atom or a C_{1-5} alkyl, C_{2-5} alkenyl (particularly allyl), phenyl or benzyl radical; R* is a hydrogen atom or a C_{1-5} alkyl or C_{2-5} alkenyl radical or together with R° forms a methylene group doubly bonded to the carbon atom or a cyclopropane ring; R° is a hydrogen atom, except when it is combined with R* to form a methylene radical or a

[*Price*

cyclopropane ring; R is a hydrogen or fluorine atom or a hydroxy, C_{1-5} alkyl, C_{1-5} alkoxy, C_{2-5} alkenyl, polyfluoroalkyl, nitro, amino, morpholino, N-methylpiperizino, bishydroxyethylamino, C_{1-6} alkanoylamino, N-(C_{1-5} alkyl)-C_{1-6} alkanoylamino, C_{1-5} alkyl amino, di(C_{1-5} alkyl)amino, N-pyrrolidinyl, N-azacyclopropyl, cyano, aminomethyl, dimethyl - aminomethyl, dialkylsulphonamido, benzylmercapto, or mercapto radical; and M is a hydroxy, amino, benzyloxy, C_{1-5} alkoxy, or OZ radical where Z is a cation.

The invention also provides 2,3-dihydro derivatives of these compounds, and a method of preparing them.

A critical feature of the new compounds of this invention is the presence of an aroyl or hetero-aroyl radical attached to the N—1 position of the indole. These acyl groups may be further substituted in the aromatic ring with substituents of the types mentioned above, particularly those substituents that can be regarded as functional. In the preferred compounds, the N—1 aroyl radical is benzoyl and a functional substituent is in the para position of the six-membered ring. Furyl, thienyl, pyrryl, thiazolyl, thiadiazolyl, pyrazinyl, pyridyl, alkylpyridyl, pyrazolyl, imidazolyl, oxazolyl, pyrimidinyl and isoxazolyl are examples of suitable heterocyclic radicals.

The α-(3-indolyl)-aliphatic acids of this invention may be derivatives of acetic, propionic, butyric, valeric, acrylic or 4-pentenoic acid. The esters, which are important intermediates in the synthesis of the free acids, and in many cases are themselves of importance as end products, include the methyl, ethyl, propyl, *t*-butyl and benzyl esters.

The salts of these new acids can be obtained by treatment of the free acid with base under mild conditions. In this manner there may be obtained alkali metal salts such as those of sodium and potassium, the aluminium or magnesium salts or salts of alkaline-earth metals, such as those of barium and calcium. Salts of organic amines such as dimethylamine, morpholine, methyl cyclohexylamine or glucosamine may be obtained by reacting the acid with the appropriate organic base. The amides of the new acids are conveniently synthesized by first preparing the amide of an α-(3-indolyl)-lower aliphatic acid unsubstituted at the 1-position and then acylating it by the process described below. Such amides are conveniently obtained by reacting the free acid with urea or treating the appropriate acid chloride with ammonia.

The 2-position of the indole ring nucleus (R^{11} in the formula above) may be occupied by a hydrogen atom although it is preferred that there be present at this position of the molecule a C_{1-5} alkyl radical, such as methyl, ethyl, propyl or butyl.

The following compounds are representative of those contemplated by this invention and which may be prepared by the procedure discussed hereinbelow:

Methyl α - (1 - *p* - chlorobenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl) - acetate;
methyl α - (1 - *p* - chlorobenzoyl - 2,5-dimethyl-3-indolyl)-acetate;
methyl α - (1 - *p* - methylthiobenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl) - acetate;
α - (1 - *p* - chlorobenzoyl - 2 - methyl - 5-methoxy-3-indolyl)-propionic acid;
α - (1 - *p* - chlorobenzoyl - 2 - methyl - 5-methoxy-3-indolyl)-acetamide;
α - (1 - benzoyl - 2 - methyl - 5 - methoxy-3-indolyl)-acetamide;
ethyl α - [1 - (2,4 - dichlorobenzoyl) - 2-methyl - 5 - methoxy - 3 - indolyl] - propionate;
methyl α - [1 - (2^1 - thenoyl) - 2 - methyl-5-methoxy-3-indolyl]-acetate;
benzyl [1 - (4^1 - thiazolyl) - 2 - ethyl - 5-methyl-3-indolyl]-propionate;
benzyl α - [1 - (2^1 - furoyl) - 2,5 - dimethyl-3-indolyl]-propionate;
propyl α - [1 - (nicotinoyl) - 2 - methyl-5-methoxy-3-indolyl]-acetate;
benzyl α - 1 - (naphthoyl) - 2 - methyl - 5-methoxy-3-indolyl]-acetate; and
α - [1 - (4^1 - thiazolyl) - 2 - methyl - 5-methoxy-3-indolyl]-propionamide.

The α-(1-aroyl or hetero-aroyl-3-indolyl)-lower aliphatic acids and their derivatives described herein are synthesized by acylation of the α-(3-indolyl)-lower aliphatic acid, ester or amide having the desired substituents at the 2- and 5-positions of the ring nucleus. It is preferred to carry out the acylation on an ester or amide derivative of the lower aliphatic acid. In those cases where the free acid is desired, the ester may be converted under suitable reaction conditions to the free acid. It has been observed that the 1-aroyl or hetero-aroyl substituent is easily hydrolysed under conditions normally used for saponification of an ester to the free acid. For this reason, care must be taken in converting the α-(1-aroyl or hetero-aroyl-3-indolyl)-lower aliphatic acid esters to the corresponding free acids. It has been found that one convenient method of accomplishing this conversion comprises acylation of the benzyl ester and subsequent hydrogenolytic removal of the benzyl group, e.g. by agitating a solution of the ester in an inert solvent with a catalytic amount of palladium in an atmosphere of hydrogen. Alternatively, other esters such as the *t*-butyl esters, which are amenable to selective removal by other treatment, such as heating, e.g. above 210° C. or at 25—110° C. in the presence of a catalytic amount of an aryl sulphonic acid or other acids, may be used. When, instead of an ester, the amides of these acids are prepared, the free acids are formed by reaction of the amides with a stoichiometric

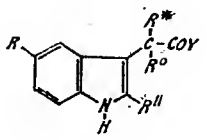
quantity of nitrous acid in an inert solvent.

The acylation reaction is preferably conducted by treating the α-(3-indolyl)-lower aliphatic acid starting material with an alkali metal hydride such as sodium hydride to form e.g. a sodium salt and then intimatcly contacting the salt with an aroyl or hetero-aroyl acid halide in an anhydrous inert solvent medium. It is preferred to use solvents such as dimethylformamide, dimethylformamide-benzene, benzene, toluene or xylene. It is preferred to carry out the acylation at about room temperature although lower temperatures may be used if the particular reactants are unduly susceptible to decomposition.

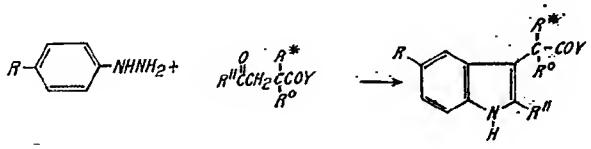
An alternative method of acylating the 1-position is by use of a phenolic ester of the acylating acid such as the *p*-nitrophenyl ester. This latter is prepared by mixing the acid and *p*-nitrophenol in tetrahydrofuran and adding dicylohexyl carbodiimide in tetrahydrofuran slowly. The dicyclohexylurea which forms is removed by filtration and the nitrophenyl ester is recovered from the filtrate. Alternatively, there can also be used the anhydride, azide or thiophenolic ester of the acylating acid. The acylation of the α-(3-indolyl)-lower aliphatic acid starting material is achieved by forming a sodium salt of said material with sodium hydride in an anhydrous solvent and adding the acylating agent.

The α-(1-aroyl or hetero-aroyl-3-indolyl)-lower aliphatic acid compounds of the invention have a high degree of anti-inflammatory activity and are effective in the prevention and inhibition of granuloma tissue formation. Certain of them possess this activity in high degree and are of value in the treatment of arthritic and dermatological disorders and in like conditions which are responsive to treatment with anti-inflammatory agents. In addition, the compounds of this invention have a useful degree of antipyretic activity. For these purposes, they are normally administered orally in tablets or capsules, the optimum dosage depending, of course, on the particular compound being used and the type and severity of infection being treated. Although the optimum quantities of these compounds of this invention to be used in such a manner will depend on the compound and the particular type of disease or condition being treated, oral dose levels of preferred compounds in the range of 1.0—2000 mg. per day are useful in control of arthritic conditions, depending on the activity of the specific compound and the reaction sensitivity of the patient.

The indolyl aliphatic acid compounds used as starting material in the reaction discussed above, and having the formula:



where R^{11}, R*, R° and R have the previously defined meanings and Y is a C_{1-5} alkoxy, a benzyloxy or an amino radical, may be synthesized in various ways. When R^{11} is hydrogen or methyl it is preferred to form such compounds by reacting together an appropriately substituted phenylhydrazine (III) and a compound of Formula IV to form an intermediate phenylhydrazone which cyclizes under the reaction conditions to the indole compound



III IV V

where R*, R°, R^{11}, R and Y are as above. The reaction is normally carried out in a lower alkanol such as methanol, ethanol, isopropanol or butanol containing an acid such as hydrochloric, hydrobromic, sulphuric or acetic acid or in aqueous mineral acid such as concentrated hydrochloric, hydrobromic, sulphuric or acetic acid, or other Lewis acids such as $ZnCl_2$, BF_3, $SnCl_4$ and the like. The acid serves as a catalyst in the condensation and ring closure reactions leading to the indole compound V. When Compound IV is an ester, the nature of the ester is not critical, although it is preferred to use a lower alkyl ester, e.g. the methyl, ethyl, propyl, isobutyl or isopropyl compound. To avoid the possibility of transesterification the alcohol used as the solvent medium is preferably the same as the alcohol moiety of the ester. When R^{11} is hydrogen, it is convenient to use the aldehyde in the form of an acetal, e.g. methyl γ,γ-dimethoxy butyrate. An acid-addition salt of the phenylhydrazine reactant, for example the hydrochloride, is normally preferred over the free base for practical reasons, although such salts and the base are equivalent in the reaction itself.

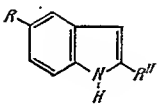
Formation of the α-(3-indolyl)-aliphatic

acid, or its ester, is brought about at elevated temperatures, good results being obtained by refluxing the reaction mixture for at least about 15 minutes. Longer reaction times are not harmful and may be used if desired. The desired compound is recovered from the reaction mixture and purified by techniques such as solvent extraction, chromatography and/or distillation. Since the esters of Formula V are low melting solids, they are conveniently purified by distillation under reduced pressure. They are saponified by treatment with an alkali metal hydroxide.

The substituted phenylhydrazines used as one of the starting materials in this synthesis are prepared by known methods. One convenient method is by diazotization of the appropriately substituted aniline to give the diazo compound, treatment of the latter with stannous chloride to form a tin complex, and decomposition of this complex to the phenylhydrazine with sodium hydroxide.

The 1-acyl group in α-(1-acyl-3-indolyl) aliphatic acids and esters of this invention is, as has been mentioned earlier, easily hydrolysed under the conditions normally used to saponify an ester. For this reason, the benzyl esters of the intermediate α-(1-unsubstituted-3-indolyl) acids are convenient starting materials. These are obtained by forming the free α-(1-unsubstituted-3-indolyl) aliphatic acid and esterifying this with benzyl alcohol in an inert solvent with an acid catalyst (sulphuric and arylsulphonic acids, etc.). Alternatively, the intermediate benzyl ester is synthesized directly by using the benzyl ester of the proper laevulinic acid in the original synthesis of the indole ring, or is formed by base-catalysed ester exchange from other esters. After acylation of the indole nitrogen of these benzyl ester intermediates, the benzyl group can be removed clearly by hydrogenolysis, a process which leaves the 1-acyl group untouched.

Alternatively, it is possible to first produce an indole of the formula:



VI

where R^{11} and R have the same meaning, and then introduce the carboxylic acid residue at the 3-position. This is accomplished by treating the indole of Formula VI under Mannich reaction conditions with formaldehyde-dialkylamine to produce a substituted gramine, subsequently reacting this latter compound with an alkali metal cyanide in a lower alkanol, and finally hydrolysing with a strong base such as sodium or potassium hydroxide.

While this method of introducing the aliphatic acid residue at the 3-position after elaboration of the indole ring is, of course, generally applicable to compounds having the structure shown above, it is particularly useful for making compounds of this invention where R^{11} is a C_{1-5} alkyl radical other than methyl, such as the 2-ethyl or 2-propyl. Compounds of Formula VI are readily prepared following the procedures set forth in the literature.

Products where R is fluorine, cyano, C_{1-5} alkyl, nitro or C_{1-5} alkoxy are prepared via the synthesis beginning from a substituted 2-nitro benzaldehyde or 2-nitrotoluene.

The 2,3-dihydro derivatives are prepared by subjecting the corresponding 2,3-unsaturated compound to catalytic hydrogenation, e.g. over a nickel catalyst at room temperature.

The synthesis of various compounds of this invention having on the indole ring system a 5-substituent which has a nitrogen attached to the homocyclic ring of the indole is generally based on the 5-nitro compound. This is transformed into the desired 5-substituent. Such transformation may be before or after acylation of the 1-position, depending on the extent to which the desired 5-substituent may interfere with the acylation. If such interference is possible, the 1-acylation should be carried out on the 5-nitro indole and the nitro later transformed into the desired 5-substituent. Such transformation can be carried out in a number of ways. Reduction of the 5-nitro groups gives a 5-amino group. Reaction of the amino with alkyl halides give mono and dialkyl amino groups. If the alkyl halide is a dihaloalkylene group (e.g. 1,4-dibromobutane) a heterocyclic ring (e.g. pyrrolidino) is formed. Similarly, bis(β-chlorethyl) ether will give an N-morpholino compound. Alkylation can also be carried out simultaneously with reduction, as e.g. with formaldehyde or with Raney nickel and hydrogen. Acylation can similarly be carried out on the 5-amino compounds or on the 5-nitro (with simultaneous reduction) to give 5-acylamino compounds. The 5-amino group can be reacted with isocyanates to give 5-ureido compounds.

—The following examples, in which all temperatures are given on the Centigrade scale, are given for purposes of illustration. Examples 1, 14 to 16 and 21 are preparations of starting materials and do not exemplify the invention.

EXAMPLE 1.

A. Ethyl α-(2-methyl-5-methoxy-3-indolyl)-propionate.

A solution of 25 g. of *p*-methoxyphenylhydrazine hydrochloride and 20 g. of ethyl α-methyl laevulinate in 250 ml. of 2*N* ethanolic hydrochloric acid is heated on a steam bath for a few minutes. An exothermic reaction takes place with the separation of ammonium chloride. The reaction flask is removed from

the steam bath and the mixture allowed to reflux gently until the initial reaction subsides. The mixture is again heated on a steam bath under reflux for 30 minutes, and then concentrated *in vacuo* to a volume of about 80 ml. The concentrate is diluted with about 400 ml. of water and extracted with ether. The resulting ethereal extract is washed with a saturated solution of sodium bicarbonate and with water, and dried over anhydrous sodium sulphate. The dried solution is filtered and evaporated to a dark brown syrup which is purified by chromatography over about 1 lb. of acid-washed alumina in a column $2\frac{1}{4}$ inches in internal diameter using mixtures of ether and petroleum ether (v/v 1:9 to 1:1) as eluent. The light yellow syrup so obtained is distilled in a short-path distillation apparatus and the product collected at b.p. 150—153° C. (0.25 mm.). The distillate of ethyl α - (2 - methyl - 5 - methoxy - 3 - indolyl)-propionate crystallizes on trituration with petroleum ether, m.p. 53—55.5° C. On recrystallization from a mixture of ether and petroleum ether the melting point is unchanged.

Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36.
Found: C, 69.23; H, 7.31; N, 5.60.

When the methyl, propyl, isopropyl or benzyl ester of α-methyl laevulinic acid is used in the above reaction in place of the ethyl ester, there is obtained methyl α-(2-methyl - 5 - methoxy - 3 - indolyl) - propionate, propyl α - (2 - methyl - 5 - methoxy-3 - indolyl) - propionate, isopropyl α - (2-methyl - 5 - methoxy - 3 - indolyl) - propionate, or benzyl α - (2 - methyl - 5-methoxy-3-indolyl)-propionate, respectively. Alternatively, when an ester of laevulinic acid is used as a starting material in the above process, the corresponding ester of α-(2-methyl - 5 - methoxy - 3 - indolyl) - acetic acid is obtained.

B. Ethyl α-(2,5-dimethyl-3-indolyl)-propionate.

20 g. of *p*-methylphenylhydrazine hydrochloride and 20 g. of ethyl α-methyl laevulinate are added to 250 ml. of 2*N* ethanolic hydrogen chloride and the mixture warmed until the reaction sets in. After the initial exothermic reaction stops, the mixture is refluxed for about $\frac{1}{2}$ hour and then concentrated *in vacuo* to about $\frac{1}{3}$ volume. 400 ml. of water are added and the aqueous solution extracted with ether. The ethereal extracts are washed with sodium bicarbonate solution and with water, then dried over sodium sulphate. The ethereal solution is concentrated to a small volume *in vacuo* and chromatographed over acid-washed alumina (1 lb. of alumina in a column $2\frac{1}{4}$ inches in internal diameter). The material eluted with mixtures of ether and petroleum ether (v/v 9:1 to 1:1) is distilled in a short-path distillation apparatus. Ethyl α-(2,5-dimethyl-3-indolyl)-propionate distils at 150—170° (bath temp.)/1 mm., and crystallizes on trituration with petroleum ether, m.p. 88—88.5° C.

When a lower alkyl or benzyl laevulinate is used in place of ethyl α-methyl laevulinate, lower alkyl or benzyl (2,5-dimethyl-3-indolyl)-acetate is produced.

EXAMPLE 2.

Ethyl α-(1-*p*-methylthiobenzoyl-2-methyl-5-methoxy-3-indolyl)-propionate.

2.3 g. (0.046 mole) of 50% sodium hydride in mineral oil is suspended in 250 ml. of dimethylformamide and the suspension is stirred for 20 minutes under nitrogen with ice-cooling. Then 8.64 g. (0.035 mole) of ethyl α - (2 - methyl - 5 - methoxy - 3-indolyl)-propionate is added and the mixture stirred for 20 minutes. 8.6 g. (0.046 mole) of *p*-methylthiobenzoyl chloride in 50 ml. of dimethylformamide is added dropwise over a period of 30 minutes. The mixture is stirred in an ice-bath for 5 hours under nitrogen. It is then poured into a mixture of 500 ml. of ether, 5 ml. of acetic acid and 1 litre of iced water. The organic products are extracted with 3 x 300 ml. of ether. The ethereal solutions are combined and washed with a large quantity of water, and dried over sodium sulphate. The solution is filtered, evaporated to near dryness and the residue charged onto a 300-g. alumina column. The ethyl α-(1-*p*-methylthiobenzoyl - 2 - methyl - 5 - methoxy-3-indolyl)-propionate is eluted with 10% ether in petroleum ether. It is obtained as a yellow oil on concentration of the eluates to dryness.

The *p*-methylthiobenzoyl chloride starting material is obtained by heating a mixture of 27 g. (0.15 mole) of *p*-methylthiobenzoic acid and 21.4 g. (0.18 mole) of thionyl chloride on a steam bath for 1 hour. About 20 ml. of benzene is then added and boiled off. The remaining solution is centrifuged and diluted with petroleum ether. On cooling, the acid chloride separates, m.p. 40—44° C.

When methyl (2 - methyl - 5 - methoxy-3-indolyl)-acetate is used as the starting material in the above process, there is obtained methyl (1-*p*-methylthiobenzoyl-2-methyl-5-methoxy-3-indolyl)-acetate.

EXAMPLE 3.

Methyl α-(1-*p*-chlorobenzoyl-2-methyl-5-methoxy-3-indolyl)-acetate.

To 3.9 g. (00.078 mole) of 51% sodium hydride in mineral oil suspended in 150 ml. of distilled dimethylformamide, in a 1-litre 3-neck flask, is added with stirring at 0° C., 9.5 g. (0.040 mole) of methyl (2-methyl-5-methoxy-3-indolyl)-acetate in 150 ml. of dimethylformamide. The mixture is allowed to stir for one hour and then 9.1 g. (0.052 m.) of *p*-chlorobenzoyl chloride in 50 ml. of dimethylformamide is added dropwise over a period of 30 minutes. The reaction mixture is stirred another 30 minutes at 0° C. and then allowed to stand for 12 hours in the cold.

The reaction mixture is then filtered and the solids washed with ether. The ether is added to the filtrate which is then washed with water and dried over sodium sulphate. After filtering off the sodium sulphate, approximately 75 g. of acid-washed alumina is added to the ethereal solution and this mixture concentrated to dryness. The indole-coated alumina is then packed on top of a column of 400 g. of alumina. The column is eluted with petroleum ether containing increasing amounts of ethyl ether. Methyl α-(1-*p* - chlorobenzoyl - 2 - methyl - 5 - methoxy-3-indolyl)-acetate is eluted with 15% ether in petroleum ether. These latter eluates are combined and concentrated to dryness. Recrystallization of the residue from a mixture of benzene and petroleum ether yields substantially pure methyl α-(1-*p*-chlorobenzoyl-2 - methyl - 5 - methoxy - 3 - indolyl)-acetate, m.p. 99—100° C.

Carrying out the above-noted process with ethyl α - (2 - methyl - 5 - methoxy - 3-indolyl) - propionate or benzyl α - (2,5-dimethyl - 3 - indolyl) - propionate yields, respectively, ethyl α - (1 - *p* - chlorobenzoyl - 2 - methyl - 5 - methoxy - 3-indolyl)-propionate and benzyl α-(1-*p*-chlorobenzoyl - 2,5 - dimethyl - 3 - indolyl) - propionate.

EXAMPLE 4.

Ethyl α-[1-(*o*-methyl-*p*-methylthiobenzoyl)-2 - methyl - 5 - methoxy - 3 - indolyl]-Propionate.

A mixture of 100 ml. of dimethylformamide, 5.2 g. (0.02 mole) of ethyl α-(2-methyl - 5 - methoxy - 3 - indolyl) - propionate and 1.2 g. (0.025 mole) of sodium hydride in mineral oil (50% dispersion) is stirred in an ice-bath under nitrogen for 1 hour. A solution of 4.0 g. (0.02 mole) of 2-methyl-4-methylthiobenzoyl chloride (prepared from the acid, m.p. 159—162° C., and thionyl chloride) and 25 ml. of dimethylformamide is then added during 0.5 hour, and stirring is continued for 16 hours at room temperature. The mixture is poured into 350 ml. of water, extracted with ether, and the ethereal solution washed with water, dried over magnesium sulphate, filtered and evaporated to dryness under reduced pressure. The residual oil is dissolved in petroleum ether (60—70° C.) and chromatographed on 250 g. of acid-washed alumina. The ethyl α-[1 - (*o* - methyl - *p* - methylthiobenzoyl)-2 - methyl - 5 - methoxy - 3 - indolyl]-propionate is eluted with 15% ether in petroleum ether and isolated as an oil. I.R. $\lambda_{max}^{CHCl_3}$ 5.77 (CO), 5.94 (CO), 6.21, 6.73.

EXAMPLE 5.

Ethyl α-(1-benzoyl-2-methyl-5-methoxy-3-indolyl)-propionate.

To a solution of 5.22 g. of ethyl α-(2-methyl-5-methoxy-3-indolyl)-propionate in 20 ml. of dimethylformamide is added a suspension of 1.2 g. of 51% sodium hydride in mineral oil in 40 ml. of dimethylformamide. After 1 hour of stirring at room temperature, a solution of 2.88 ml. of benzoyl chloride in 10 ml. of dimethylformamide is added to initiate a mild exothermic reaction with precipitation of sodium chloride. The reaction mixture is stirred for 6 hours and then allowed to stand overnight. The mixture is poured into about 200 g. of ice and extracted with ether three times. The ethereal solution is washed with water and aqueous sodium bicarbonate and dried over potassium carbonate. After filtration the solution is evaporated to a syrup and chromatographed on a column of 100 g. of acid-washed alumina, using mixtures of benzene and petroleum ether (2:1 to 3:1 v/v) as eluent. A total of 1.06 g. of ethyl α-(1-benzoyl-2-methyl - 5 - methoxy - 3 - indolyl) - propionate is obtained as a thick yellow oil. The infrared spectrum shows no N—H absorption near the 2.8—3μ region but shows strong C=O absorptions at 5.8 and 5.95μ characteristic for ester and amide functional groups, respectively.

EXAMPLE 6.

Ethyl α-(1-*p*-chlorobenzoyl-2-methyl-5-methoxy-3-indolyl)-propionate.

13 g. of ethyl (2-methyl-5-methoxy-3-indolyl)-propionate is added to a mixture of 2.5 g. of 51% sodium hydride in mineral oil (emulsion) in 240 ml. of dimethylformamide. The resulting mixture is stirred at room temperature for 30 minutes and then a solution of 8.75 g. of *p*-chlorobenzoyl chloride in 50 ml. of dimethylformamide is added slowly to it over a 40-minute period. The mixture is then stirred in an ice-bath for 4 hours under nitrogen. It is then poured into a mixture of ether, acetic acid and water as described in Example 2. Following the work-up procedure, using a 200-g. column of alumina for the chromatography step, and eluting with a 1:1

mixture of benzene and petroleum ether, ethyl α - (1 - *p* - chlorobenzoyl - 2 - methyl - 5-methoxy-3-indolyl)-propionate is obtained as a yellow oil.

EXAMPLE 7.

(1-benzoyl-2-methyl-5-methoxy-3-indolyl)-acetic Acid.

A. A solution of 15 g. of methyl (2-methyl - 5 - methoxy - 3 - indolyl) - acetate and 0.2 g. of sodium in 60 ml. of benzyl alcohol is slowly fractionated over a period of 4½ hours through a Vigreux column to remove methanol. The excess of benzyl alcohol is then removed by distillation at 60° C. and a pressure of 2.5 mm. of mercury to give a residue of 18.6 g. of benzyl (2-methyl-5-methoxy-3-indolyl)-acetate.

B. 10 g. of the benzyl ester obtained above is added to 3.3 g. of 51% sodium hydride mineral oil emulsion in 260 ml. of dimethylformamide according to the procedure of Example 2. This mixture is treated as described in that example in 7.7 ml. of benzoyl chloride and the reaction mixture worked up by the above-described process using a chromatographic column of 340 g. of alumina and eluting with 20—30% ether in petroleum ether. From these eluates there is obtained benzyl (1 - benzoyl - 2 - methyl - 5-methoxy-3-indolyl)-acetate, m.p. 91—92° C.

C. 1.5 g. of the ester obtained in Part B above is added to 20 ml. of ethyl acetate containing a drop of acetic acid and reduced catalytically at room temperature in the presence of palladium-on-charcoal catalyst. When the reduction is complete the catalyst is removed by filtration and the filtrate evaporated to a crystalline residue. This residue is recrystallized from aqueous ethanol to give 1 - benzoyl - (2 - methyl - 5-methoxy-3-indolyl)-acetic acid, m.p. 172—173° C. Alternatively, the residue obtained on removal of the reaction solvent may be purified by dissolving it in chloroform and precipitating it by addition of petroleum ether to the chloroform solution.

EXAMPLE 8.

Ethyl α-(1-*p*-fluorobenzoyl-2-methyl-5-methoxy-3-indolyl)-propionate.

10.5 g. of ethyl α-(2-methyl-5-methoxy-3-indolyl)-propionate is added to a suspension of 2.2 g. of 51% sodium hydride in mineral oil (emulsion) in 240 ml. of dimethylformamide. After stirring for 25 minutes, 7.5 g. of *p*-fluorobenzoyl chloride is added slowly over a 40-minute period, and the resulting mixture stirred for 40 minutes at 10—15° C. The reaction mixture is then poured into 400 ml. of water and the product isolated as described in Example 4 to give substantially pure ethyl α-(1-*p*-fluorobenzoyl-2-methyl-5-methoxy-3-indolyl)-propionate.

When the above process is carried out by reacting the sodium salt of methyl α-(2-methyl - 5 - methoxy - 3 - indolyl) - propionate with *p* - trifluoromethylbenzoyl chloride, there is obtained methyl α-(1-*p*-trifluoromethylbenzoyl - 2 - methyl - 5-methoxy-3-indolyl)-propionate.

EXAMPLE 9.

The corresponding N—1 aroyl or heteroaroyl derivatives of benzyl α-(2-methyl-5-methoxy-3-indolyl)-propionate and benzyl (2-methyl - 5 - methoxy - 3 - indolyl) - acetate are obtained by reacting together in equimolar amounts and according to the procedure of Example 3, the sodium salts of these esters and one of the compounds:

3,4,5-trimethoxy benzoyl chloride;
p-phenoxy benzoyl chloride;
p-trifluoroacetyl benzoyl chloride;
p - N,N - dimethylsulphamoyl benzoyl chloride;
3-furoyl chloride;
1 - methylimidazole - 5 - carboxylic acid chloride;
1,3 - dimethyl - 2,3 - dihydro - 2 - oxo-imidazole-4-carboxylic acid chloride;
1 - methyl - benzimidazole - 2 - carboxy chloride;
5-fluoro-2-thenoyl chloride;
3-thenoyl chloride;
5-nitro-2-furoyl chloride;
1 - methylindazole - 3 - carboxy chloride;
1 - methyl - 6 - nitroindazole - 3 - carboxy chloride;
oxazole-4-carboxy chloride;
benzoxazole-2-carboxy chloride;
thiazole-4-carboxy chloride;
thiazole-2-carboxy chloride;
2-phenylthiazole-4-carboxy chloride;
2 - benzylmercaptothiazole - 4 - carboxy chloride;
p-acetylbenzoyl chloride;
N,N - dimethyl - *p* - carboxamidobenzoyl chloride;
p-cyanobenzoyl chloride;
p-carbomethoxybenzoyl chloride;
p-formylbenzoyl chloride;
p-trifluoromethylthiobenzoyl chloride;
p - N,N - dimethylsulphamoylbenzoyl chloride;
p-methylsulphinylbenzoyl chloride;
p-methylsulphonylbenzoyl chloride;
p-benzylthiobenzoyl chloride;
p-mercaptobenzoyl chloride;
p-nitrobenzoyl chloride;
p-dimethylaminobenzoyl chloride;
p-acetamidobenzoyl chloride;
o-fluoro-*p*-chlorobenzoyl chloride;
o-methoxy-*p*-chlorobenzoyl chloride;
o-hydroxy-*p*-chlorobenzoyl chloride;
2,4,5-trichlorobenzoyl chloride.

The resulting 1-substituted indolyl esters are converted to the corresponding free acids by the procedure of Example 7C.

EXAMPLE 10.
1-p-chlorobenzoyl-2-methyl-5-methoxy-3-indolyl-acetic acid.

A. 2-methyl-5-methoxy-3-indolylacetic anhydride.

10 g. (0.049 mole) of dicyclohexylcarbodiimide is dissolved in a solution of 22 g. (0.10 mole) of 2-methyl-5-methoxy-3-indolylacetic acid in 200 ml. of tetrahydrofuran, and the solution is allowed to stand at room temperature for 2 hours. The precipitated urea is removed by filtration, and the filtrate is evaporated *in vacuo* to a residue and flushed with Skellysolve B. The residual oily anhydride is used without purification in the next step.

B. *t*-butyl 2-methyl-5-methoxy-3-indolyl-acetate.

25 ml. of *t*-butyl alcohol and 0.3 g. of fused zinc chloride are added to the anhydride from part A. The solution is refluxed for 16 hours and excess of alcohol is removed *in vacuo*. The residue is dissolved in ether, washed several times with saturated aqueous sodium bicarbonate, water, and saturated aqueous salt solution. After drying over magnesium sulphate, the solution is treated with charcoal, evaporated, and flushed several times with Skellysolve B for complete removal of alcohol. The residual oily ester (18 g., 93%) is used without purification.

C. *t*-butyl 1-*p*-chlorobenzoyl-2-methyl-5-methoxy-3-indolylacetate.

A stirred solution of 18 g. (0.065 mole) of the ester obtained in Part B in 450 ml. of dry dimethylformamide is cooled to 4° in an ice bath, and sodium hydride (4.9 g., 0.098 mole) (50% susp.) is added in portions. After 15 minutes, *p*-chlorobenzoyl chloride (15 g., 0.085 mole) is added dropwise during 10 minutes, and the mixture is stirred for 9 hours without replenishing the ice bath. The mixture is then poured into 1 l. of 5% acetic acid, extracted with a mixture of ether and benzene, washed thoroughly with water, aqueous sodium bicarbonate and saturated aqueous salt solution, dried over magnesium sulphate, treated with charcoal, and evaporated to a residue which partly crystallizes. This is shaken with ether, filtered, and the filtrate is evaporated to a residue (17 g.) which solidifies after being refrigerated overnight. The crude product is boiled with 300 ml. of Skellysolve B, cooled to room temperature, decanted from some gummy material, treated with charcoal, concentrated to 100 ml., and allowed to crystallize. 10 g. of the product thus obtained is recrystallized from 50 ml. of methanol and gives 4.5 g. of analytically pure material, m.p. 103—104°.

D. 1-*p*-chlorobenzoyl-2-methyl-5-methoxy-3-indolylacetic acid.

A mixture of 1 g. ester and 0.1 g. powdered porous plate is heated in an oil bath at 210° with magnetic stirring under a blanket of nitrogen for about 2 hours. No intensification of colour (pale yellow) occurs during this period. After cooling under nitrogen, the product is dissolved in benzene and ether, filtered, and extracted with aqueous sodium bicarbonate. The aqueous solution is filtered with suction to remove ether, neutralized with acetic acid, and then acidified weakly with dilute hydrochloric acid. The crude product (0.4 g., 47%) is recrystallized from aqueous ethanol and dried *in vacuo* at 65°; m.p. 151°.

EXAMPLE 11.
1-p-methylthiobenzoyl-2-methyl-5-methoxy-3-indolyl-α-propionic acid.

A. 2-methyl-5-methoxy-3-indolyl-α-propionic anhydride.

9 g. (0.044 mole) of dicyclohexylcarbodiimide is dissolved in a solution of 21 g. (0.09 mole) of 2-methyl-5-methoxy-3-indolyl-α-propionic acid in 200 ml. of tetrahydrofuran and the solution is allowed to stand at room temperature for 2 hours. The precipitated urea is removed by filtration, and the filtrate is evaporated *in vacuo* to a residue and flushed with Skellysolve B. The residual oily anhydride is used without purification.

B. *t*-butyl 2-methyl-5-methoxy-3-indolyl-α-propionate.

25 ml. of *t*-butyl alcohol and 0.3 g. of fused zinc chloride are added to the above anhydride. The solution is refluxed for 16 hours, and excess of alcohol is removed *in vacuo*. The residue is dissolved in ether, washed several times with saturated aqueous sodium bicarbonate, water and saturated aqueous salt solution. After drying over magnesium sulphate the solution is treated with charcoal, evaporated, and flushed several times with Skellysolve B for complete removal of alcohol. The residual oil ester (14 g.) is used without purification.

C. *t*-butyl 1-*p*-methylthiobenzoyl-2-methyl-5-methoxy-3-indolyl-α-propionate.

A stirred solution of 20 g. (0.69 mole) of the ester obtained in part B in 450 ml. of dry dimethylformamide is cooled to 4° in an ice bath and 5.2 g. (0.10 mole) of a 50% suspension of sodium hydride is added in portions. After the mixture has been stirred for 10 minutes, 17 g. (0.091 mole) of *p*-methylthiobenzoyl chloride (m.p. 51°) is added in portions during 10 minutes, and the mixture is stirred for 7 hours at room tem-

perature without replenishing the ice bath. The mixture is then poured into 1 l. of 5% acetic acid, extracted with ether, washed thoroughly with water, aqueous sodium bicarbonate, and saturated aqueous salt solution, dried over magnesium sulphate, treated with charcoal, and evaporated *in vacuo* to a residue (33 g.). This is dissolved in ether, mixed with 100 g. of acid-washed alumina, and evaporated *in vacuo* to dryness. The residue is placed above a column of 300 g. of acid-washed alumina in Skellysolve B. After washing with Skellysolve B, the product is eluted with 5% ether in Skellysolve B, and is obtained as a yellow oil (11 g., 36%).

D. 1-*p*-methylthiobenzoyl-2-methyl-5-methoxy-3-indolyl-α-propionic acid.

The pyrolysis is carried out in the same manner as with *t*-butyl 1-*p*-chlorobenzoyl-2-methyl-5-methoxy-3-indolyl acetate (of Example 10 D). The product is recrystallized from a mixture of aqueous ethanol and Skellysolve B; m.p. 175—6°.

EXAMPLE 12.

1-*p*-chlorobenzoyl-2-methyl-5-methoxy-3-indolyl-α-propionic acid.

A. To a solution of 20.0 g. (0.07 mole) of *t*-butyl α-(2-methyl-5-methoxy-3-indolyl)-propionate in 270 ml. dimethylformamide is added in small portions 7.0 g. (0.14 mole) of 51% sodium hydride in mineral oil under nitrogen with stirring and ice-cooling. After 15 minutes, 17.5 g. (0.10 mole) of the *p*-chlorobenzoyl chloride is added dropwise, a white precipitate separates out almost immediately. The mixture is stirred at 0° for 2 hours and is allowed to stand in the cold room overnight. The next morning the mixture is filtered and diluted with ether. Half of the solution is washed successively with water, aqueous sodium bicarbonate, and water, and dried over sodium sulphate. The dried solution is concentrated to a syrup which is chromatographed on 400 g. of acid-washed alumina. Mineral oil and trace impurities are eluted by petroleum ether and 5% ether in petroleum ether, and the desired product then is obtained by elution with 10% ether in petroleum ether as yellow oil. The other half of the solution is similarly treated.

B. The above ester and a few pieces of porous plate chips are placed in a flask submerged in an oil bath. A steady stream of nitrogen is introduced into the test tube through the opening while the temperature of the oil bath is slowly raised to 215°. After half an hour at 215°, the mixture is dissolved in ether, filtered and washed with aqueous sodium bicarbonate. The bicarbonate extract is acidified with dilute hydrochloric acid, and the precipitate is taken into ether, washed with water, dried over sodium sulphate and evaporated to dryness. The solid residue is recrystallized from a mixture of benzene and petroleum ether to give the desired acid, m.p. 87—88°.

EXAMPLE 13.

Methyl (1-isonicotinoyl-2-methyl-5-methoxy-3-indolyl)-acetate.

A. In a 500-ml. round-bottom flask (all equipment flame-dried) is added 13.9 g. of *p*-nitrophenol and 12.3 g. isonicotinic acid in 250 ml. dry tetrahydrofuran. Through a dropping funnel is added over 30 minutes 20.6 g. of dicyclohexylcarbodiimide in 100 ml. of dry tetrahydrofuran. The reaction is allowed to run overnight with stirring. The dicyclohexylurea which forms during the reaction is filtered. The filter cake is washed with dry tetrahydrofuran. The solution is evaporated to dryness. The solid is taken up in benzene and washed with sodium bicarbonate solution and then with water and dried over anhydrous sodium sulphate. The solution is concentrated under vacuum to dryness. The solid *p*-nitrophenylisonicotinate is then recrystallized from benzene, m.p. 126—127° C.

B. In a 250-ml. round-bottom flask (flame-dried equipment) is placed at 0° C. with nitrogen, 100 ml. of dry dimethylformamide with 10.5 g. of methyl α-(2-methyl-5-methoxy-3-indolyl)-acetate. To this is added 2.5 g. of 50% sodium-hydride-in-mineral-oil mixture. After the mixture has been stirred for 30 minutes, there is added over 15 minutes a solution of 11 g. of *p*-nitrophenyl isonicotinate in 50 ml. of dry dimethylformamide. The reaction mixture is stirred for 4 hours at 0° C. under nitrogen followed by stirring under nitrogen at room temperature overnight. The reaction mixture is then poured into an ice-water-ether mixture containing a few ml. of acetic acid and the layers are separated. The aqueous phase is washed with ether and the ethereal extracts are combined. To the ethereal layers is added a saturated solution of hydrogen chloride gas in dry ether. The ether is decanted off, leaving a heavy oil. The oil is washed with ether; aqueous sodium bicarbonate solution is then added and the product is extracted with ether. The ethereal layer is dried over anhydrous sodium sulphate and concentrated to dryness. The product is crystallized from dry ether, m.p. 114—115° C.

Microanalysis:

Calc.	C, 67.45;	H, 5.37;	N, 8.28.
Found:	C, 67.67;	H, 5.50;	N, 8.14.

EXAMPLE 14.

Methyl (2-methyl-5-nitro-3-indolyl)acetate.

A solution of 40 g. of laevulinic acid in 300 ml. of hot water is added to a solution of 65 g. of *p*-nitrophenylhydrazine hydrochloride in 700 ml. of hot water with

stirring. After about half an hour the hydrazone derivative is collected in a filter, washed with water and dried at 110° *in vacuo*. The yield is 84 g., m.p. 175—179°.

42 g. of the above hydrazone is added to a solution of 120 g. of fused zinc chloride in 100 ml. of absolute ethanol and the mixture is refluxed for 18 hours. The cooled solution is poured into dilute hydrochloric acid with stirring, and the insoluble gummy material separated is extracted with hot ethanol. The ethanolic extract is evaporated *in vacuo* to a syrup, which is redissolved in ether. The ethereal solution is extracted with 10% aqueous sodium carbonate several times. Acidification of the aqueous solution gives a crude product which recrystallizes from chloroform to give (2-methyl-5-nitro-3-indolyl)acetic acid, m.p. 238°.

The above acid is treated with a mixture of 3 g. of sulphuric acid and 40 ml. of methanol at the reflux temperature for 6 hours. The methyl ester is obtained as a yellow crystalline product, m.p. 132—40° after recrystallization from benzene.

Similarly, methyl α-(2-methyl-5-nitro-3-indolyl)-propionate is prepared by using an equivalent amount of α-methyl-laevulinic acid as the starting material.

EXAMPLE 15.

Methyl(2-methyl-5-amino-3-indolyl)acetate.

3 g. of methyl(2-methyl-5-nitro-3-indolyl)-acetate is dissolved in 300 ml. of dry methanol and reduced in hydrogen in an autoclave with Raney nickel as catalyst. After the theoretical amount of hydrogen has been taken up, the catalyst is removed by filtration. The catalyst and reaction flask are washed with methanol. The methanol solution is evaporated to dryness. The product is crystallized from benzene, m.p. 144—145°.

Microanalysis:
Calc. C, 66.03; H, 6.47; N, 12.84.
Found: C, 65.96; H, 6.29; N, 12.56.

EXAMPLE 16.

Methyl [2-methyl-5-(1¹-pyrrolidino)-3-indolyl]acetate.

In a 125 ml. flask is placed 80 ml. of ethanol. To this is added 1.0 g. of methyl (2-methyl - 5 - amino - 3 - indolyl)acetate, 0.99 g. of 1,4-dibromobutane and 0.975 g. of anhydrous sodium carbonate. This mixture is stirred at reflux temperature in a nitrogen atmosphere for 6 hours. The reaction mixture is then filtered and the filtrate is concentrated *in vacuo* to a small volume and diluted with ether. This solution is then washed with water twice, dried with anhydrous sodium sulphate and concentrated *in vacuo* to dryness. The product is absorbed on 6 g. of silica gel. The product is then chromatographed over 30 g. of silica gel using as elutant ether containing 25% or less by volume of petroleum ether. The eluted material is combined and crystallized from a mixture of benzene and Skellysolve B. m.p. 117—118° C.

Microanalysis:
Calc. C, 70.56; H, 7.40; N, 10.29.
Found: C, 70.77; H, 7.72; N, 10.00.

When ethylene dibromide is used instead of dibromobutane, the product obtained is the 5-(1-azacyclopropyl)indolyl compound.

EXAMPLE 17.

Methyl (1-*p*-chlorobenzoyl-2-methyl-5-(1¹-pyrrolidino)-3-indolyl acetate.

In a dry 125-ml. flask is placed 1.2 g. of methyl(2 - methyl - 5 - (1¹ - pyrrolidino)-3-indolyl) acetate in 60 ml. of dry dimethylformamide. To this solution, cooled to 0° C. is added 0.23 g. of 50% sodium hydride slurry in mineral oil. This mixture is stirred for 30 minutes. Then a solution of 0.8 g. of *p*-chlorobenzoyl chloride diluted with 5 ml. of dry dimethylformamide is added dropwise. This reaction is stirred for 4 hours at 0° C. under a nitrogen atmosphere. The reaction mixture is then stirred overnight at room temperature under a nitrogen atmosphere. The reaction mixture is added to an ice-water-ether mixture containing a few milliliters of acetic acid.

The ethereal layer is separated and the aqueous layer is washed with ether. The combined ethereal layers are washed once with aqueous sodium carbonate and twice with water, dried over anhydrous sodium sulphate and evaporated *in vacuo* to an oil. The product is absorbed on 10 g. of silica gel and chromatographed from 60 g. silica gel. The product is collected using mixtures of ether and petroleum ether in a v/v ratio from 1:3 to 1:1. The combined material is crystallized from ether, m.p. 62—64°.

EXAMPLE 18.

Methyl-(1-*p*-chlorobenzoyl-2-methyl-5-nitro-3-indolyl)-acetate.

In a dried 250-ml. flask is placed 3.9 g. of methyl (2-methyl-5-nitro-3-indolyl)-acetate in 125 ml. dry dimethylformamide. To this solution cooled to 0° C. is added 0.8 g. of 50% sodium hydride in mineral oil. This is stirred under nitrogen for 30 minutes. To this is added dropwise 2.75 g. of *p*-chlorobenzoyl chloride in 15 ml. of dry dimethylformamide over a 5-minute period. The reaction mixture is stirred 4 hours at 0° C. under nitrogen and then stirred overnight at room temperature under nitrogen. It is then poured into an ice-water-benzene mixture containing a few milliliters of acetic acid. The benzene layer is separated and the aqueous layer is washed with benzene. The combined

benzene layers are washed with aqueous sodium bicarbonate and water, dried over anhydrous sodium sulphate and concentrated to dryness *in vacuo*. The product is crystallized from a mixture of benzene and Skellysolve B. m.p. 170—171°.

Microanalysis:
Calc.: C, 59.00; H, 3.91; N, 7.24.
Found: C, 59.24; H, 4.00; N, 7.39.

The corresponding propionate is formed when an equivalent amount of the corresponding methyl α - (2 - methyl - 5 - nitro - 3-indolyl)propionate prepared in Example 14 is used as the starting material.

EXAMPLE 19.

Methyl (1-*p*-chlorobenzoyl-2-methyl-5-dimethylamino-3-indolyl) acetate.

To a solution of 0,387 g. of methyl α-(1-*p* - chlorobenzoyl - 2 - methyl - 5 - nitro-3-indolyl) acetate in 20 ml. of distilled dimethoxyethane is added 1.5 ml. of glacial acetic acid and 0.5 ml. of a 37% solution of aqueous formaldehyde. This mixture is reduced with Raney nickel at 40 psi and room temperature. After the theorctical amount of hydrogen has reacted, the reaction mixture is filtered, concentrated *in vacuo* to a small volume and diluted with ether. The ethereal solution is washed with aqueous sodium bicarbonate and then with water, dried with anhydrous sodium sulphate and concentrated *in vacuo* to an oil.

Microanalysis:
Calc.: C, 65.50; H, 5.50; N, 7.28.
Found: C, 65.66; H, 5.91; N, 7.46.

EXAMPLE 20.

Methyl (1-*p*-chlorobenzoyl-2-methyl-5-acetamido-3-indolyl)acetate.

To 0.388 g. of methyl (1-*p*-chlorobenzoyl-2 - methyl - 5 - nitro - 3 - indolyl) acetate in 30 ml. of anhydrous ethyl acetatc is added 0.306 g. acetic anhydride. The mixture is reduced with Raney nickel at room temperature and 40 p.s.i. After the theoretical amount of hydrogen has bccn absorbed, the catalyst is removed by filtration. The solution is concentrated *in vacuo* to a small volume and poured into an ice-water-ether mixture. The ethereal layer is separated and the aqueous layer is washed with ether. The combined ethereal extracts are washed with sodium bicarbonate followed by water, dried with anhydrous sodium sulphate and concentrated *in vacuo* to dryness. The product is crystallized from benzene and ether, m.p. 176—177° C.

Microanalysis:
Calc.: C, 63.25; H, 4.80; N, 7.02.
Found: C, 63.40; H, 4.82; N, 6.89.

EXAMPLE 21.

Benzyl (2-methyl-5-nitro-3-indolyl)acetate.

In a dry 250-ml. flask is placed 80 ml. dry benzene and 20 ml. benzyl alcohol. To this are added 3.0 g. of 2-methyl-5-nitro-3-indolyl acetic acid and 0.2 g. of *p*-toluenesulphonic acid. The resulting slurry (which clears on hcating) is heated to reflux under nitrogen. The water formed during the reaction is collected in a Stark and Dean tube. The reaction is stopped when the distillate is clear (about 2 hours). The excess of benzyl alcohol is removed *in vacuo*. The residue is dissolved in benzene and washed with sodium bicarbonate followed by water, dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The product is absorbed on 15 g. of acid-washcd alumina and chromatographed over 75 g. of acid-washed alumina. The product is eluted with 1:1 to 3:1 mixtures (v/v) of ether and benzene. Thc eluatc is evaporated and the combined product is crystallizcd from benzene and Skellysolve B m.p. 147—148°.

Microanalysis:
Calc.: C, 66.66; H, 4.97; N, 8.64.
Found: C, 66.83; H, 4.77; N, 8.52.

EXAMPLE 22.

Benzyl (1-*p*-chlorobenzoyl-2-methyl-5-nitro-3-indolyl)acetate.

In a dry 125 ml. flask is placed 3.0 g. of benzyl (2 - methyl - 5 - nitro - 3 - indolyl)-acetate in 60 ml. of dry dimethylformamide. To this solution, cooled to 0° C. in a nitrogen atmosphere, is added 0.475 g. of 50% sodium hydride-in-mineral oil. This is stirred for 30 minutes. Then 1.65 g. of *p*-chlorobenzoyl chloride in 10 ml. of dry dimethylformamide is added dropwise over a 5-minute period. The reaction mixture is stirred at 0° C. for 4 hours under a nitrogen atmosphere followed by stirring at room temperature under nitrogen overnight. It is then poured into an ice-water-benzene mixture. The benzene layer is separated and the aqueous layer is washed with benzenc. The combined benzene extracts are washed with aqueous sodium bicarbonate followed by water, dried with anhydrous sodium sulphate and concentrated *in vacuo* to dryness. The product is crystallized from mixtures of benzene and Skellysolve B m.p. 166—167° C.

Microanalysis:
Calc.: C, 64.86; H, 4.14; N, 6.05.
Found: C, 64.78; H, 4.22; N, 5.91.

EXAMPLE 23.

Methyl α-(1-*p*-chlorobenzoyl-2-methyl-5-amino-3-indolyl) propionate.

0.025 mole of methyl α-(1-*p*-chlorobenzoyl-2-methyl-5-nitro-3-indolyl) propionate in 100 ml. of ethanol is hydrogenated in the presence

of 120 mg. of 10% palladium-on-charcoal catalyst at 40 p.s.i. at room temperature. After 0.075 mole of hydrogen has been consumed, the hydrogenation is stopped, and the solution filtered to remove the catalyst. The filtrate is concentrated to dryness *in vacuo* to give methyl α - (1 - *p* - chlorobenzoyl - 2-methyl-5-amino-3-indolyl) propionate.

EXAMPLE 24.

Methyl α-[1-*p*-chlorobenzoyl-2-methyl-5-(N-methyl-acetamido)-3-indolyl] acetate.

Methyl - 1 - *p* - chlorobenzoyl - 2 - methyl-5 - (5 - acetamido - 3 - indolyl) - acetate is added to a suspension of sodium hydride in dimethylformamide with stirring and ice-cooling. After one hour methyl iodide is added and the mixture is stirred overnight. The reaction mixture is poured into ice-water and extracted with ether. Evaporation of the ethereal solution and chromatography of the residual oil on an alumina column, using 15—25% (v/v) ether in petroleum ether as the eluent, gives methyl 1-*p*-chlorobenzoyl-2-methyl - 5 - (N - methyl acetamido) - 3-indolyl acetate.

EXAMPLE 25.

A. Methyl [1-*p*-chlorobenzoyl-2-methyl-5-bis(β-hydroxyethyl)amino-3-indolyl]acetate.

A mixture of 0.02 mole of methyl α-(1-*p*-chlorobenzoyl - 2 - methyl - 5 - amino - 3-indolyl)propionate, 0.044 mole of ethylene oxide and 0.03 mole of acetic acid in 300 ml. dimethoxyethane is heated to 100° for 18 hours in an autoclave. The mixture is then diluted with water and filtered to yield crude methyl [1 - *p* - chlorobenzoyl - 2 - methyl-5 - bis(β - hydroxyethyl)amino - 3 - indolyl]-propionate.

B. Methyl [1-*p*-chlorobenzoyl-2-methyl-5-(4¹-methyl-1¹-piperazinyl)-3-indolyl]acetate.

The product of A is stirred at 0° in pyridine with two mole proportions of *p*-toluenesulphonyl chloride until the reaction is substantially complete. The mixture is poured into water and the 5-bis(*p*-toluenesulphonyl-oxyethyl)amino compound is isolated. This is dissolved in benzene and one mole proportion of methylamine is added. The mixture is allowed to stand at room temperature for 3 days. The mixture is poured into iced water containing two equivalents of sodium carbonate and extracted with ether immediately. Evaporation of the ether yields methyl [1 - *p* - chlorobenzoyl - 2 - methyl - 5 - (4¹-methyl - 1¹ - piperazinyl) - 3 - indolyl]-acetate.

Either of the above products, when used in the procedure of Example 7, gives the corresponding free acid.

EXAMPLE 26.

Methyl [1-*p*-chlorobenzoyl-2-methyl-5-(4¹-morpholinyl)-3-indolyl]acetate.

A solution of paratoluenesulphonyl chloride (0.1 mole) in 200 ml. of benzene is added dropwise with stirring to a solution of methyl α - [1 - *p* - chlorobenzoyl - 2 - methyl - 5-bis(β - hydroxyethyl)amino - 3 - indolyl]-acetate (0.1 mole) and pyridine (0.3 mole) in 300 ml. benzene at room temperature over a period of one hour. The mixture is then heated under reflux for 3 hours, washed with water, dried over sodium sulphate and evaporated to a syrup. Chromatography of the syrup on an alumina column using 30—50% (v/v) ether in petroleum ether as the eluent gives methyl [1-*p*-chlorobenzoyl-2-methyl - 5 - (4¹ - morpholinyl) - 3 - indolyl]-acetate.

The above product, when used in the procedure of Example 7, gives the corresponding free acid.

EXAMPLE 27.

A. 2-methyl-5-cyano-3-indolyl acetic acid methyl ester.

A solution of *p*-cyano phenylhydrazine (0.1 mole) and laevulinic acid (0.1 mole) in 200 ml. concentrated hydrochloric acid is heated at 90° for 20 minutes and diluted with iced water (400 ml.). The crude product which separates is extracted with ether and chromatographed on a silica gel column to give 2-methyl-5-cyano-3-indolyl acetic acid using 20—50% (v/v) ether and petroleum ether as the eluent.

The methyl ester is prepared by treatment with diazomethane in ether until the yellow of diazomethane persists and the mixture is evaporated.

B. Methyl α-(1-*p*-chlorobenzoyl-2-methyl-5-cyano-3-indolyl)acetate.

Acylation of the ester (prepared in Example 26A above) in dimethylformamide with sodium hydride and *p*-chlorobenzoyl chloride, by the procedure of Example 2, gives methyl (1 - *p* - chlorobenzoyl - 2 - methyl - 5-cyano-3-indolyl)acetate.

C. Methyl α-(1-*p*-chlorobenzoyl-2-methyl-5-aminomethyl-3-indolyl)acetate.

The 5-cyano ester prepared in Example 27B is hydrogenated in ethanol in the presence of Raney nickel and 3 moles of anhydrous ammonia at 2000 p.s.i. at room temperature to give, after filtration of the catalyst and evaporation of the reaction mixture, methyl (1 - *p* - chlorobenzoyl - 2 - methyl - 5-aminomethyl-3-indolyl)acetate which can be recrystallized from aqueous ethanol.

D. Methyl (1-*p*-chlorobenzoyl-2-methyl-5-dimethylaminomethyl-3-indolyl)acetate.

Treatment of the above α-aminomethyl indole with 2 moles of methyl iodide gives the 5-dimethylaminomethyl derivative.

E. When the products of Examples 27C and 27D above are used in the procedure of Example 7, the corresponding free acids are obtained.

EXAMPLE 28.

α-(1-*p*-methylmercaptobenzoyl-2-methyl-5-methoxy-3-indolyl)-butyric acid.

When the procedures of Examples 1 and 2 are followed using ethyl α-ethyl laevulinate in place of ethyl α-methyl laevulinate, there are obtained successively ethyl α-(2-methyl-5-methoxy - 3 - indolyl) - butyrate and ethyl α - (1 - *p* - methylmercaptobenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl) - butyrate. When the latter product is used in the procedure of Example 7 the corresponding butyric acid derivative is obtained.

The starting ethyl α-ethyl laevulinate is prepared by alkylation of the sodio derivative of ethyl acetoacetate in ethanol with 1 mole of ethyl α-bromobutyrate, followed by hydrolysis and decarboxylation. The α-ethyl laevulinic acid obtained is re-esterified with 2*N* ethanolic hydrogen chloride at reflux temperature for 18 hours.

EXAMPLE 29.

6.5 g. (0.02 mole) of α-(1-benzoyl-2-methyl-5-methoxy-3-indolyl)-acetic acid is added to 50 ml. of water which has been flushed with nitrogen. The slurry is stirred under nitrogen and 20 ml. of 1.05*N* sodium carbonate added with stirring. When a clear solution is obtained, a solution of 2.2 g. of $Al_2(SO_4)_3.18H_2O$ in 8 ml. of water is added with vigorous stirring. The mixture is stirred until it is homogeneous and the solid aluminium salt of (1-benzoyl-2-methyl-5-methoxy-3-indolyl)acetic acid, is recovered by filtration and washed with water and with ethanol.

In a similar fashion, there may be prepared the sodium and aluminium salts as well as other salts, such as the potassium, iron and magnesium salts, of the various (3-indolyl) aliphatic acids described in the accompanying examples.

EXAMPLE 30.

Ethyl α-(1-benzoyl-2-methyl-5-methoxy-3-indolyl) acrylate.

A. 500 ml. of dry ether, 36.02 g. of triphenyl-phosphonium bromide and 94.36 ml. of 1.10*N* n-butyl lithium are stirred for 1 hour at room temperature under nitrogen. 38 g. of ethyl (2 - methyl - 5 - methoxy - 3 - indolyl) glyoxylate in 260 ml. of benzene and 500 ml. of dry ether are added, and stirring continued for 1 hour. The reaction mixture is transferred to a pressure flask and heated in a closed flask at 65—70° C. for 5 hours. The liquid is poured from the pressure flask and the gum triturated with 500 ml. of 33% benzene in ether. The solutions are combined and washed with three 500-ml. portions of water, dried over sodium sulphate, filtered and concentrated *in vacuo* to a syrup. The syrup is slurried in benzene and charged onto a 200 g. column of activated alumina. Ethyl α - (2 - methyl - 5 - methoxy - 3 - indolyl)-acrylate is eluted by washing the column with 30% ether in petroleum ether and removing the eluting solvents by evaporation.

The procedure of Example 13B is then followed using *p*-nitrophenylbenzoate in equivalent quantities in place of the *p*-nitrophenyl-isonicotinate, to give ethyl α-(1-benzoyl-2-methyl-5-methoxy-3-indolyl)-acrylate.

EXAMPLE 31.

Ethyl α-(1-benzoyl-2-methyl-5-methoxy-3-indolyl)-cyclopropyl carboxylate.

1.8 g. of ethyl α - (1 - benzyl - 2-methyl-5-nitro-3-indolyl)-acrylate in 10 ml. of dry tetrahydrofuran is added to 4 g. of diazomethane, 1.25 g. of zinc-copper couple and 0.2 g. of iodine in 20 ml. of dry tetrahydrofuran. The mixture is refluxed under nitrogen with stirring for 20 hours. The reaction mixture is then filtered, the filtrate added to ice water, and the whole extracted with three 50-ml. portions of ether. The combined ether extracts are washed with two 50-ml. portions of water, dried over sodium sulphate, filtered, and concentrated. The syrup thus obtained is poured on to a 60 g. alumina column as a slurry in benzene. Ethyl α-(1-benzoyl-2-methyl - 5 - methoxy - 3 - indolyl) - cyclopropylcarboxylate is collected from the column by elution with 60% ether-petroleum ether.

EXAMPLE 32.

The corresponding N—1 aroyl or hetero-aroyl derivatives of benzyl α-(2-methyl-5-methoxy - 3 - indolyl)propionate, benzyl (2-methyl - 5 - methoxy - 3 - indolyl)acetate and benzyl (2 - methyl - 5 - nitro - 3-indolyl)acetate are obtained by reacting these esters by the procedure of Example 13B with the *p*-nitrophenyl esters of the following acids, the *p*-nitrophenyl esters having been obtained from the acids by the procedure of Example 13A, using in each case the equivalent amount of the selected acid in place of the isonicotinic acid used in 13A and of its nitrophenyl ester used in 13B and equivalent quantities of the indolyl esters:

1-methylpyrrolyl-2-carboxylic acid;
5-methylpyrazole-3-carboxylic acid;
1,5 - dimethyl - 4 - bromopyrazole - 3-carboxylic acid;

1-phenylpyrazole-4-carboxylic acid;
1-phenyl-5-pyrazolone-3-carboxylic acid;
2 - phenyl - 5 - methyloxazole - 4-carboxylic acid;
isoxazole-3-carboxylic acid;
5-phenylisoxazole-3-carboxylic acid;
1,2-benzoisothiazole-3-carboxylic acid;
1,2,3-thiadiazole-4-carboxylic acid;
1 - methyl - 1,2,3 - triazole - 4 - carboxylic acid;
nicotinic acid;
picolinic acid;
isonicotinic acid-N-oxide;
3-chloroisonicotinic acid;
6-methoxynicotinic acid;
6-phenylnicotinic acid;
α-pyrone-5-carboxylic acid;
pyridazine-4-carboxylic acid;
3 - keto - 4 - methyl - 2 - phenyl - 2,3-dihydropyridazine-6-carboxylic acid;
cinnoline-4-carboxylic acid;
2 - methylmercapto - 4 - chloropyrimidine-5-carboxylic acid;
2,4-dichloropyrimidine-5-carboxylic acid;
pyrazinoic acid;
5-methoxypyrazinoic acid;
p-difluoromethoxy benzoic acid (prepared by the action of difluorochloromethane on the *p*-hydroxybenzoate of benzyl alcohol followed by hydrogenation of the benzyl group). The esters so obtained are converted to the free acids by the procedure of Example 7C.

Example 33.
Ethyl α-(1-*p*-chlorobenzoyl-2-methyl-5-ethoxy-3-indolyl)propionate.

The procedure of Example 1A is followed using an equivalent quantity of *p*-ethoxyphenylhydrazine hydrochloride in place of the methoxyphenylhydrazine to give ethyl α-(2-methyl - 5 - ethoxy - 3 - indolyl)propionate. When this is used in the procedure of Example 3 there is obtained ethyl α-(1-*p*-chlorobenzoyl - 2 - methyl - 5 - methoxy - 3-indolyl)propionate. This product, when used in the procedure of Example 7, yields the corresponding free α-indolyl propionic acid.

Similarly, when *p*-propoxy and *p*-butoxy phenylhydrazine are used in the above procedures, the correspondingly 5-substituted indolyl acids are obtained.

When the procedure of Example 1A is followed using in place of the *p*-methoxyphenylhydrazine, equivalent amounts of *p*-ethylphenylhydrazine, *p*-butylphenylhydrazine and *p*-fluorophenylhydrazine (each obtainable by the diazotization of the corresponding *p*-substituted aniline and reduction of the diazo) and the resultant indolyl ester is acylated by the procedure of Example 3 and further treated by the procedure of Example 7, the corresponding 5-substituted indolyl esters and acids are obtained.

When the procedure of Examples 1A, 3 and 7 are followed starting with phenylhydrazine, the corresponding 5-unsubstituted indolyl esters and acids are produced.

Example 34.
1-benzoyl-2-methyl-5-methoxy-3-indolyl-acetamide.

To a suspension of 1.0 g. of 50% sodium hydride in 80 ml. benzene is added 4.4 g. of 2 - methyl - 5 - methoxy - 3 - indolylacetamide with stirring. 20 ml. of dimethylformamide is then added, followed, 20 minutes later, by 2.8 g. benzoyl chloride. The reaction mixture is stirred at room temperature for 1 hour and then poured into 400 ml. of ice and water. The precipitate is collected on a filter, m.p. 215—218°. The crude product is recrystallized from ethyl acetate twice, m.p. 219—220°. Its ultra-violet absorption spectrum in ethanol shows maxima at λ max 2675 Å, E, 1%, 406 and λ max 3160 Å, E, 1% 188. Characteristic of a N-benzoyl indole chromophore.

Microanalysis:
Calcd.: $C_{19}H_{18}N_2O_3$: C, 71.24; H, 5.03.
Found: C, 71.00; H, 5.35.

Example 35.
1-benzoyl-2-methyl-5-methoxy-3-indolyl-acetic acid.

To a solution of 3.2 g. of 1-benzoyl-2-methyl - 5 - methoxy - 3 - indolylacetamide in 50 ml. dimethoxyethane containing 1 ml. of 12*N* hydrochloric acid at 0° is added 0.7 g. of sodium nitrite with stirring. After gas evolution has subsided the mixture is poured into 200 ml. of iced water and the precipitate is extracted with methylene chloride. The methylene chloride solution is extracted with sodium bicarbonate solution. Acidification of the aqueous solution with 2*N* hydrochloric acid precipitates the desired acid which is purified by recrystallization from benzene and from ethyl acetate-Skellysolve B.

Example 36.
The acylation procedures of Examples 3 of Example 12A are followed using various aromatic acyl chlorides in equivalent quantities in place of *p*-chlorobenzoyl chloride and using, as necessary, esters of 2-methyl-5-methoxy-3-indolyl acetic acid or of α-(2-methyl - 5 - methoxy - 3 - indolyl)propionic acid. Some of the resulting esters are converted to the corresponding free acid by the method of Example 7 or 12B as indicated below. Where the method of Example 12B is used, the 1-acylation is by the process of Example 12A. The products obtained by these experiments are:—

1 - *p* - methoxybenzoyl - 2 - methyl - 5-methoxy-3-indolyl)acetic acid, m.p. 88—89° C. (free acid by method of Example 7);

α - (1 - *p* - methoxybenzoyl - 2 - methyl-5 - methoxy - 3 - indolyl)propionic acid, m.p. 65° C. (free acid by method of Example 7);

methyl (1 - *p* - bromobenzoyl - 2 - methyl-5 - methoxy - 3 - indolyl)acetate, m.p. 106—107.5° C.;

methyl (1 - *p* - nitrobenzoyl - 2 - methyl-5 - methoxyl - 3 - indolyl)acctate, m.p. 130—132° C.;

methyl (1 - *o* - chlorobenzoyl - 2 - methyl-5 - methoxy - 3 - indolyl)acetate, m.p. 91—93° C.;

methyl (1 - *m* - chlorobenzoyl - 2 - methyl-5 - methoxy - 3 - indolyl)acetate, m.p. 51—52° C.;

methyl (1 - *p* - phenylbenzoyl - 2 - methyl-5 - methoxy - 3 - indolyl)acetate, m.p. 101.5—103° C.;

methyl (1 - *p* - acetoxybenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl)acetate, m.p. 99—101° C.;

ethyl [1 - (4 - thiazolylcarbonyl) - 2-methyl - 5 - methoxy - 3 - indolyl)acetate, m.p. 76—82° C.;

ethyl [1 - (2 - thenoyl) - 2 - methyl - 5-methoxy-3-indolyl]acetate (oil);

t - butyl α - (1 - *p* - bromobenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl)propionate, m.p. 103—105° C.;

methyl (1 - α - naphthoyl - 2 - methyl-5 - methoxy - 3 - indolyl)acetate (oil);

methyl (1 - *p* - benzoyloxybenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl)acetate, m.p. 116—118° C.;

methyl (1 - *p* - hydroxybenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl)acetate, m.p. 155—158° C. (preparcd from the *p*-benzoyloxybenzoyl compound by catalytic hydrogenation over palladium);

methyl (1 - *o* - benzyloxybenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl)acetate (not isolated—uscd to prepare next compound by catalytic hydrogenation over palladium);

methyl (1 - *o* - hydroxybenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl)acetate (oil);

methyl (1 - *o* - fluorobenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl)acetate, m.p. 98—99° C.;

[1 - (2 - thenoyl) - 2 - methyl - 5-methoxy-3-indolyl]acetic acid, m.p. 62° (method of Example 12);

methyl (1 - β - naphthoyl - 2 - methyl-5 - methoxy - 3 - indolyl)acetate, m.p. 120—124° C.;

methyl [1 - (5 - chloro - 2 - thenoyl) - 2-methyl - 5 - methoxy - 3 - indolyl]acetate (oil);

(1 - *p* - trifluoromethylbenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl)acetic acid, m.p. 169—171° C. (method of Example 12);

methyl [1 - (2,6 - dimethoxybenzoyl) - 2-methyl - 5 - methoxy - 3 - indolyl]acetate, m.p. 139.5—141° C.;

methyl [1 - (*o*,*p* - dichlorobenzoyl) - 2-methyl - 5 - methoxy - 3 - indolyl]acetate (oil).

EXAMPLE 37.

The procedure of Example 1A is followed using an equivalent quantity of each of the following phenylhydrazines in place of the *p*-methoxyphenyl hydrazines: *p*-dimethylsulphonamidophenylhydrazine, *p*-benzylmercaptophenylhydrazine, *p* - vinyl phenylhydrazine.

When the resulting indolyl acid is acylated by the procedure of Example 3, the corresponding 1-chlorobenzoyl indolyl acids are obtained.

EXAMPLE 38.

Methyl 5 - methoxy - 3 - indolylacetate is reduced at 4000 p.s.i. of hydrogen over a nickel catalyst at room tempcrature. The resultant methyl 5 - methoxy - 2,3 - dihydro-3-indolyl acetate is acylated by the procedure of Example 3 to give methyl (1-*p*-chlorbenzoyl - 5 - methoxy - 2,3 - dihydro-3-indolyl)acetate. When this is stirred at room temperature in 100 times its weight of a 0.1*N* solution of sodium hydroxide in 95% ethanol, the corresponding free acid is obtained.

Any of the other indole acids prepared in accordance with the Examples may be reduced to the 2,3-dihydro derivatives by an analogous method.

EXAMPLE 39.

0.07 mole of phenylhydrazine and 0.08 mole of mcthyl γ,γ-dimethoxybutyrate are added to 250 ml. of 2*N* ethanolic hydrogen chloride and the mixture is warmed until reaction sets in. After the initial exothermic reaction stops, the mixture is refluxed for about 30 minutes and then concentrated *in vacuo* to about ⅓ volume. 400 ml. of water is added and the aqueous solution is extracted with ether. The ethereal extracts are washed with sodium bicarbonate solution and with water and then dried over sodium sulphate. The ethereal solution is concentrated to a small volume *in vacuo* and chromatographed over 200 grams of acid-washed alumina. The material is eluted with a mixture of ether and petroleum ether (v/v 50—60%) and distilled in a short-path distillation apparatus to produce methyl 3-indolyl-acetate. This product is then used in the procedure of Example 3 to produce methyl 1-*p*-chlorobenzoyl-3-indolyl-acetate.

EXAMPLE 40.

1-p-Chlorobenzoyl-2-benzyl-3-indolyl-acetic acid.

Step A. 2-Benzyl-3-indolyl acetic acid.

2 - Benzyl - 3 - indolyl - acetic acid is prepared, using the method of A. Stoll *et al,* Helv. Chim. Acta *38* 1452 (1955), starting with the known 2-benzylindole (J.C.S. *1954* 2582).

Step B. 2-Benzyl-3-indolyl-acetic anhydride.

Dicycloheptylcarbodiimide (10 g, 0.049 m) is dissolved in a solution of 2-benzyl-3-indolylacetic acid (26.5 g, 0.10 m) in 200 ml THF and allowed to stand at room temperature for 2 hours. The precipitated urea is removed by filtration and the filtrate is evaporated *in vacuo* to a residue and flushed with Skellysolve B. The residual anhydride is used without purification in the next step.

Step C. t-Butyl 2-benzyl-3-indolyl-acetate.

t-Butyl alcohol (25 ml) and fused zinc chloride (0.3 g) are added to the anhydride from part A, the solution is refluxed for 16 hours, and the excess of alcohol is removed *in vacuo*. The residue is dissolved in ether and washed several times with saturated salt solution. After drying over magnesium sulphate the solution is treated with charcoal, evaporated and flushed several times with Skellysolve B for complete removal of the alcohol. The residual ester is used without purification.

Step D. t-Butyl 1-*p*-chlorobenzoyl-2-benzyl-3-indolyl acetate.

A stirred solution of the product of Step C (20.9 g, 0.065 m) in dry DMF (450 ml) is cooled to 4° in an ice bath and sodium hydride (4.9 g, 0.098 m, 50% suspension) is added in portions. After 15 minutes, the *p*-chlorobenzoyl chloride (15 g, 0.085 m) is added dropwise during 10 minutes, and the mixture is stirred for 9 hours without replenishing the ice bath. The mixture is then poured into 1 litre of 5% acetic acid, extracted with a mixture of ether and benzene, washed thoroughly with water, sodium bicarbonate solution, and saturated salt solution, dried over magnesium sulphate, treated with charcoal and evaporated to a residue. This is shaken with ether and filtered, and the filtrate evaporated to a residue. The crude product is chromatographed on 600 g. of acid-washed alumina using a mixture (V/V 10—50%) of ether and petroleum ether as eluant.

Step E. 1-*p*-Chlorobenzoyl-2-benzyl-3-indolyl-acetic acid.

A mixture of 1 g of the product of Step D and 0.1 g powdered porous plate is heated in an oil bath at 210° C with magnetic stirring, under nitrogen for about 2 hours. After cooling under nitrogen, the product is dissolved in benzene and ether, filtered and extracted with sodium bicarbonate solution. The aqueous solution is filtered by suction to remove ether, neutralized with acetic acid, then acidified weakly with dilute hydrochloric acid. The crude product is recrystallized from aqueous ethanol and dried *in vacuo*.

EXAMPLE 41.

Step A. Methyl 2-phenyl-5-methoxy-3-indolyl-acetate.

A mixture of 0.145 mole of anhydrous sodium acetate and 0.183 mole of *p*-methoxyphenyl hydrazine hydrochloride in 150 ml of methanol is stirred under nitrogen for 30 minutes.

3-Benzoyl-propionic acid, 0.142 mole, in 80 ml. methanol is added and the mixture is stirred for 1 hour.

Anhydrous hydrogen chloride, 0.50 mole, in 125 ml methanol is added over 20 min. After heating on steam bath for 2 hours, the mixture is cooled, concentrated in vacuo taken up in 500 ml benzene, washed with 150 ml of 2.5 N-hydrochloric acid and saturated sodium bicarbonate, 150 ml, washed with 200 ml of water and dried over sodium sulphate.

Evaporation of the benzene solution and chromatography of the crude product on a 200 g column of acid-washed alumina using mixtures of ether and petroleum ether (V/V 20—50%) as eluant gives methyl 2-phenyl-5 - methoxy - 3 - indolyl - acetate, m.p. 120—120.5°.

Step B. Methyl 1-(*p*-chloro benzoyl)-2-phenyl-5-methoxy-3-indolyl-acetate.

The ester obtained in Step A (0.015 mole) is dissolved in 50 ml dimethyl formamide with ice cooling under a nitrogen atmosphere. After the addition of 0.03 mole of sodium hydride, (50% suspension in mineral oil) the suspension is stirred in an ice bath for 20 min. Then 0.022 mole of *p*-chloro benzoyl chloride in 10 ml dimethyl formamide is added and the mixture stirred overnight at a temperature below 10°.

Ether (200 ml) is added, and the resulting solution filtered and washed with 2 × 100 ml saturated sodium bicarbonate, and 2 × 100 ml water, dried over sodium sulphate and concentrated *in vacuo*. Chromatography of the product on 300 g of acid washed alumina, eluting with (V/V 30—40%) mixture of ether and petroleum ether gives methyl 1 - (*p* - chloro benzoyl) - 2 - phenyl - 5-methoxy-3-indolyl acetate as a yellow oil.

EXAMPLE 42.

Step A. 2-phenyl-5-methoxy-3-indolyl acetic acid.

The methyl 2-phenyl-5-methoxy-3-indolyl acetate (0.02 mole) obtained in Example 41

Step A is treated with 50 ml ethanol and 6 ml of 34% sodium hydroxide at reflux temperature for 3 hours. The solution is cooled and then diluted with 100 ml of water. This solution is concentrated *in vacuo* to a volume of about 100 ml and extracted with ether, (75 ml). The aqueous layer is separated and acidified with 2.5 N-hydrochloric acid and is extracted with ether (2 × 50 ml). The ethereal extracts are washed twice with 60 ml water and dried over sodium sulphate. After filtering, concentration *in vacuo* gives 2-phenyl-5-methoxy-3-indolyl acetic acid.

Step B. 2-phenyl-5-methoxy-3-indolyl acetic acid anhydride.

N,N[1] - Dicyclohexylcarbodiimide (0.05 mole) in a minimal amount of anhydrous tetrahydrofuran is added to (0.1 mole) of 2-phenyl-5-methoxy-3-indolyl acetic acid also in a minimal amount of tetrahydrofuran and the mixture is shaken vigorously for one minute, the mixture is filtered and the filtrate is concentrated *in vacuo* to give 2-phenyl-5-methoxy-3-indolyl acetic acid anhydride.

Step C. *t*-Butyl 2-phenyl-5-methoxy-3-indolyl acetate.

100 ml of *t*-butanol and 0.3 g of fused zinc chloride are added to the anhydride prepared in Step B and the mixture refluxed overnight under nitrogen. This is filtered and the solvent removed *in vacuo*. 500 ml of chloroform is added and this is washed with 2 × 200 ml saturated sodium bicarbonate, and 2 × 200 ml water, dried and concentrated to a residue. This is chromatographed on a 500 silica gel column eluting with mixtures (V/V 20—100%) of ether and petroleum ether giving *t*-butyl 2-phenyl-5-methoxy-3-indolyl acetate.

Step D. *t*-Butyl 1-*p*-chlorobenzoyl-2-phenyl-5-methoxy-3-indolyl acetate.

The *t*-butyl ester, (0.01 mole) prepared in Step C is stirred under nitrogen in 50 ml anhydrous dimethyl formamide with ice cooling and 0.012 mole of sodium hydride (50% suspension in mineral oil) is added. After 30 minutes, 0.011 mole of *p*-chlorobenzoyl chloride is added and the mixture stirred overnight at temperature <10°. 200 ml of ether is added, filtered and washed with 2 × 100 ml saturated sodium bicarbonate, 2 × 100 ml water and dried over anhydrous sodium sulphate. After filtering the solution is concentrated *in vacuo*. The product is chromatographed on a 150 g. neutral alumina column eluting with (V/V 0—05%) ethyl acetate and ether to give *t*-butyl 1-*p*-chlorobenzoyl-2-phenyl-5-methoxy-3-indolyl acetate.

Step E. 1-*p*-chlorobenzoyl-2-phenyl-5-methoxy-3-indolyl acetic acid.

A mixture of 0.005 mole of *t*-butyl 1-*p*-chlorobenzoyl - 2 - phenyl - 5 - methoxy - 3-indolyl acetate and *ca* 1 g of fine porous plate chips is heated, under nitrogen, slowly in an oil bath until isobutylene starts to escape. It is then stirred and heated at that temperature for 1 hour. After cooling, the residue is extracted with saturated sodium bicarbonate solution, and the aqueous solution washed with 100 ml chloroform made acidic with 2.5 *N* hydrochloric acid. After extracting with ether (150 ml) and washing with 2 × 75 ml water the solution is dried over anhydrous sodium sulphate. Filtering and concentrating *in vacuo* gives 1-*p*-chlorobenzoyl-2-phenyl-5-methoxy-3-indolyl acetic acid.

EXAMPLE 43.

1-p-Chlorobenzoyl-2-allyl-5-methoxy-3-indolyl acetic acid.

Step A. 5-Methoxy-2-indolyl acetaldehyde.

A solution of 5-methoxy-2-indolylacetyl chloride (0.1 mole) in dry tetrahydrofuran is treated with 0.25 mole of lithium aluminium tri-*t*-butoxy hydride with ice cooling and stirring. After the initial reaction, the mixture is stirred at room temperature for 4 hours and poured into ice. Excess of acetic acid is added and the product is extracted with ether. The ethereal solution is washed with sodium bicarbonate, dried over sodium sulphate and evaporated to a syrup. Chromatography of the residue on a column of silica gel, using ether-petroleum ether (V/V 10—30% as eluent, gives 5-methoxy-2-indolyl acetaldehyde.

Step B. 2-Allyl-5-methoxy-indole.

A solution of 0.1 mole of the aldehyde and 0.12 mole of methylene triphenylphosphine, prepared *in situ* from 0.12 mole of methyl triphenylphosphonium iodide and 0.12 mole of *n*-butyl lithium, in benzene is stirred at room temperature for 4 hours and then at 80° for 1 hour. The solution is washed with 0.5 N hydrochloric acid, water and dried over sodium sulfate. Evaporation of the solvent *in vacuo* and chromatography of the residue on a column of 300 g. acid-washed alumina, using ether-petroleum ether (v/v) 0—20% as eluent, gives 2-allyl-5-methoxy-indole.

Step C. 2-Allyl-5-methoxygramine.

A solution of 0.032 mole of 2-allyl-5-methoxy-indole in 40 ml. of dioxane is added dropwise, over 30 minutes; to an ice-cooled stirred mixture of 40 ml. dioxane, 40 ml. acetic acid, 3.2 ml. 36% aqueous formaldehyde and 8.8 ml. 25% aqueous dimethylamine. The clear solution is stirred and cooled for two hours and then allowed to warm to room temperature overnight. To this solution is added 500 ml. of water. The turbid mixture is then treated with charcoal and filtered through a silicaceous filter aid. The clear filtrate is made alkaline with 400

ml. of dilute NaOH solution and cooled in a refrigerator. The mixture is filtered and the solid gramine is washed with water and dried.

Step D. 2-Allyl-5-methoxy-3-indolyl-acetonitrile.

0.106 Mole of the gramine from part C is added to 420 ml. of methyl iodide, with vigorous stirring, over a period of 20 minutes. The reaction mixture is then allowed to remain at 5° for 15 hours. The solution is filtered and the iodine metholate cake is dried at 50° C. The solid is dissolved in a solution of 60 g. NaCN in 1 liter and warmed for 2 hours at 80°. The desired product is extracted with chloroform which is then evaporated to give a crude oily product. The oil is then dissolved in 250 ml. of ether, filtered and the filtrate is concentrated. The concentrate is diluted with petroleum ether, at which point the 2-allyl-5-methoxy-3-indolyl acetonitrile precipitates. The mixture is filtered and the cake dried.

Step E. 2-Allyl-5-methoxy-3-indolyl-acetic acid.

0.08 Mole of 2-allyl-5-methoxy-3-indolyl-acetonitrile is added to a mixture of 140 ml. of alcohol, 100 ml. of water and 4.3 g. of KOH. The mixture is refluxed 15 hours and then brought to room temperature. Glacial acetic acid (60 ml.) is added and the solution is filtered through a talc filter. The filtrate is diluted with 500 ml. of water and the precipitated 2 - allyl - 5 - methoxy - 3-indolyl-acetic acid is separated by filtration and dried.

Step F. 1-p-Chlorobenzoyl-2-allyl-5-methoxy-3-indolyl-acetic acid.

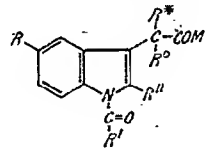
0.049 mole of dicyclohexylcarbodiimide is dissolved in a solution of 0.10 mole of 2-allyl - 5 - methoxy - 3 - indolyl - acetic acid in 200 ml. tetrahydrofuran and allowed to stand at room temperature for 2 hours. The precipitated urea is removed by filtration and the filtrate is evaporated *in vacuo* to a residue and flushed with Skellysolve B. 25 mls of *t*-butyl alcohol and 0.3 gm. of fused zinc chloride are added to the residual oily (2-allyl - 5 - methoxy - 3 - indolyl-acetic anhydride. The solution is refluxed for 16 hours and the excess alcohol is removed *in vacuo*. The residue is then dissolved in ether and washed several times with saturated salt solution. The ethereal extract is dried over magnesium sulphate and the solution treated with charcoal. The ethereal solution is then evaporated and flushed several times with Skellysolve B for complete removal of the alcohol.

.065 mole of the crude *t*-butyl ester obtained is added to 450 ml. of dimethylformamide and cooled to 4° in an ice bath. .098 mole of a 50% suspension of sodium hydride is added portionwise to this stirred solution. After 15 minutes, 0.085 mole of *p*-chlorobenzoyl chloride is added over a 10 minute interval. This mixture is then stirred for 9 hours, without replenishing the icebath. At this time, the mixture is poured into 1 litre of 5% acetic acid, extracted with a mixture of ether and benzene and washed thoroughly with water, sodium bicarbonate solution and a saturated salt solution. The ether extract is dried over magnesium sulphate, treated with charcoal and evaporated to a residue. The crude product, thus obtained, is chromatographed on 600 gms, of acid-washed alumina using a mixture of (v/v 5—50%) ether-petroleum ether as eluent, to produce *t*-butyl(1-*p*-chlorobenzoyl - 2 - allyl - 5 - methoxy - 3-indolyl)acetate.

A mixture of 1.0 g. of the latter and 0.1 g. powdered porous plate is heated, with stirring, in an oil bath at 210° C. under nitrogen for 2 hours. The product is allowed to cool under nitrogen, then dissolved in benzene and ether, filtered and extracted with sodium bicarbonate solution. The aqueous solution is filtered by suction to remove ether, neutralized with acetic acid, then acidified weakly with dilute hydrochloric acid. The crude product is then recrystallized from aqueous ethanol and dried *in vacuo*, to produce 1 - *p* - chlorobenzoyl - 2 - allyl-5-methoxy-3-indolyl-acetic acid.

WHAT WE CLAIM IS:—

1. A compound of the formula:



in which R^1 is an aromatic radical of one or two fused rings of 5 or 6 atoms each, there being not more than one heterocyclic ring and not more than three hetero atoms, the hetero atoms being oxygen, nitrogen, or sulphur, the aromatic radicals including keto dihydro aromatic radicals and the N-oxides of nitrogen heterocyclic rings, and in which aromatic radicals any substituents are halogen atoms or hydroxy, C_{1-5} alkyl, C_{1-5} alkoxy, phenyl, phenoxy, nitro, C_{1-5} alkanoylamino, di(C_{1-5} alkyl)amino, mercapto, C_{1-5} alkylthio, halo C_{1-5} alkylthio, benzylthio, benzyloxy, phenylthio, halo C_{1-5} alkyl, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, halo C_{1-6} alkanoyl, halo C_{1-5} alkoxy, cyano, di(C_{1-5} alkyl) sulphonamido, carbo C_{1-5} alkoxy, aldehyde, di(C_{1-5} alkyl)carboxamide, C_{1-5} alkylsulphinyl and C_{1-5} alkylsulphonyl radicals; R^{11} is a hydrogen atom or a C_{1-5} alkyl, C_{2-5} alkenyl, phenyl or benzyl radical; R^* is a hydrogen atom or a C_{1-5} alkyl or C_{2-5} alkenyl

radical or together with R° forms a methylene group doubly bonded to the carbon atom or a cyclopropane ring; R° is a hydrogen atom, except when it is combined with R* to form a methylene radical or a cyclopropane ring; R is a hydrogen or fluorine atom or a hydroxy, C_{1-5} alkyl, C_{1-5} alkoxy, C_{2-5} alkenyl, polyfluoroalkyl, nitro, amino, morpholino, N-methylpiperizino, bishydroxyethylamino, C_{1-6} alkanoylamino, N-(C_{1-5} alkyl)-C_{1-6} alkanoylamino, C_{1-5} alkyl amino, di-(C_{1-5} alkyl)amino, N-pyrrolidinyl, N-azacyclopropyl, cyano, aminomethyl, dimethylaminomethyl, dialkylsulphonamido, benzylmercapto, or mercapto radical; and M is a hydroxy, amino, benzyloxy, C_{1-5} alkoxy, or OZ radical where Z is a cation.

2. A 2,3 - dihydro derivative of a compound as claimed in claim 1.

3. A compound as claimed in claim 1, in which R^{11} is C_{1-5} alkyl, R* is C_{1-5} alkyl, R is C_{1-5} alkoxy, C_{1-5} alkyl or one of the substituted amino groups mentioned in claim 1, R° is hydrogen and M is hydroxyl.

4. A compound as claimed in claim 3, in which R is dimethylamino.

5. A compound as claimed in claim 3, in which R^1 is *p*-methylthiobenzoyl.

6. α - (1 - *p* - methylthiobenzoyl - 2-methyl - 5 - methoxy - 3 - indolyl)propionic acid.

7. 1 - *p* - chlorobenzoyl - 2 - benzyl - 3-indolyl-acetic acid.

8. 1 - *p* - chlorobenzoyl - 2 - phenyl - 5-methoxy-3-indolyl-acetic acid.

9. 1 - *p* - chlorobenzoyl - 2 - allyl - 5-methoxy-3-indolyl-acetic acid.

10. α - (1 - *p* - chlorobenzoyl - 2 - methyl-5-methoxy-3-indolyl)propionic acid.

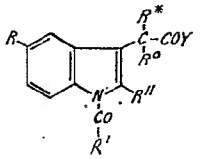
11. A compound as claimed in Claim 3, in which R^1 is *p*-chlorobenzoyl.

12. (1 - *p* - chlorobenzoyl - 2 - methyl-5-methoxy-3-indolyl)acetic acid.

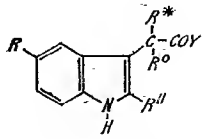
13. α - (1 - *p* - chlorobenzoyl - 2 - methyl-5-dimethylamino-3-indolyl)propionic acid.

14. (1 - *p* - chlorobenzoyl - 2 - methyl - 5-dimethylamino-3-indolyl)acetic acid.

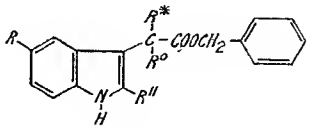
15. A process for synthesizing a compound of the formula:



in which R, R°, R^1, R^{11} and R* are as claimed in Claim 1 and Y is a C_{1-5} alkoxy, benzyloxy or amino radical, which comprises intimately contacting in an inert anhydrous solvent an aromatic acyl halide or an aromatic acyl ester of *p*-nitrophenol, the aromatic group being of the type defined for R^1 in claim 1, with the N_1 alkali metal salt of a compound of the formula:

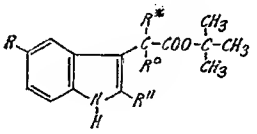


16. A process for synthesizing a compound as claimed in Claim 1 in which M represents a hydroxy group, which comprises (a) contacting intimately in an inert anhydrous solvent an aromatic carboxy halide, an aromatic carboxylic azide, an aromatic carboxylic ester of a phenol or an aromatic carboxylic ester of a thiophenol, the aromatic group being of the type defined for R^1 in Claim 1, with the N_1 alkali metal salt of a compound of the formula:



where R, R°, R^{11} and R* are as defined in Claim 1, isolating the 1-acyl-indolyl ester so produced and (b) agitating a solution of the ester in an inert solvent with a catalytic amount of palladium in an atmosphere of hydrogen.

17. A process of synthesizing a compound as claimed in Claim 1, in which M represents a hydroxy radical, which comprises contacting intimately in an inert anhydrous solvent an aromatic carboxy halide, an aromatic carboxylic azide, an aromatic carboxylic ester of a phenol or an aromatic carboxylic ester of a thiophenol, the aromatic group being of the type defined for R^1 in Claim 1, with the N_1 alkali metal salt of a compound of the formula:



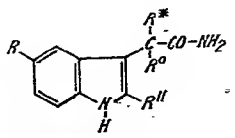
where R, R°, R^{11} and R* are as defined in Claim 1, isolating the 1-acyl indolyl ester so produced, and heating the said ester.

18. A process as claimed in Claim 17, in which the ester is heated to 25—110° C. in the presence of at least a catalytic amount of an aryl sulphonic acid.

19. A process as claimed in Claim 17, in which the ester is heated above 210° C.

20. A process for synthesizing a compound as claimed in Claim 1 in which M represents a hydroxy radical, which comprises contacting intimately in an inert anhydrous solvent an aromatic carboxy halide, an aromatic carboxylic azide, an aromatic

carboxylic cster of a phenol or an aromatic carboxylic ester of a thiophenol, the aromatic group being of the type defined for R^1 in Claim 1, with the N_1 alkali metal salt of a compound of the formula:



where R, R^o, R^* and R^{11} are as defined in Claim 1, isolating the 1-acyl indolyl acid amide so produced, and agitating the amide in an inert solvent with a stoichiometric quantity of nitrous acid.

21. A process for preparing a compound as claimed in Claim 2, which comprises subjecting a compound as claimed in Claim 1 to catalytic hydrogenation.

22. A process as claimed in Claim 21, substantially as hereinbefore described with reference to Example 38.

23. A process for preparing a compound as claimed in Claim 1, substantially as hereinbefore described with reference to any one of Examples 2 to 13, 17 to 20, 22 to 37 and 39.

24. A compound as claimed in Claim 1, when prepared by a process as claimed in any one of Claims 15 to 20 or 23 or an obvious chemical equivalent of such a process.

25. A compound as claimed in Claim 2, when prepared by a process as claimed in Claim 21 or 22 or an obvious chemical equivalent of such a process.

26. A pharmaceutical composition comprising, as active ingredient, a compound as claimed in any one of Claims 1 to 11, 24 and 25 and an inert non-toxic pharmaceutical diluent or carrier.

27. A pharmaceutical composition as claimed in Claim 26, in orally administrable form.

28. A pharmaceutical composition as claimed in Claim 27, in the form of a tablet or capsule.

29. A pharmaceutical composition as claimed in any one of Claims 26 to 28, in unit dosage containing at least 1 mg. of the active ingredient.

30. The process that comprises reacting a compound as claimed in Claim 1 or 2, in which R is an amino or monosubstituted amino group, with an isocyanate to form the corresponding 5-ureido compound.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9, Staple Inn, London, W.C.1.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1965. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.